Universidade de Aveiro
Ano 2015
Secção Autónoma de Ciências da Saúde

ANDREIA ASSUNÇÃO SOUSA DA ROCHA

ESTÁGIO CURRICULAR COMO COORDENADORA DE ESTUDOS CLÍNICOS NUM CENTRO DE INVESTIGAÇÃO CLÍNICA

CURRICULAR TRAINING AS STUDY COORDINATOR IN A CLINICAL RESEARCH CENTRE

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Dissertação apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizada sob a orientação científica do Professor Doutor Joaquim José Coutinho Ferreira, Professor Associado Convidado da Faculdade de Medicina da Universidade de Lisboa, e da Professora Doutora Alexandra Isabel Cardador de Queirós, Professora Coordenadora da Escola Superior de Saúde da Universidade de Aveiro.

Dedico este trabalho aos meus queridos pais que sempre apoiaram os meus sonhos e que sempre fizeram os possíveis e os impossíveis para os tornar realidade.

“In anything we do, any endeavour, it is not what you do, it is why you do it”

Howard Schultz

o júri

presidente	Professor Doutor Bruno Miguel Alves Fernandes do Gago Professor Auxiliar Convidado, Universidade de Aveiro
vogal - arguente	Professora Doutora Maria Joana da Costa Gomes da Silva Professora Adjunta, Universidade de Aveiro
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agradecimentos

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palavras-chave Centro de Investigação Clínica; Investigação Clínica; Ensaios Clínicos; Coordenação de Estudos Clínicos; Farmacovigilância; Escrita Científica

resumo

O presente relatório de estágio tem como objetivo descrever, em detalhe, o meu estágio curricular de dez meses na Unidade de Farmacologia Clínica do Instituto de Medicina Molecular.

Este estágio insere-se nas atividades curriculares do segundo ano do Mestrado em Biomedicina Farmacêutica da Universidade de Aveiro.

O principal foco deste estágio curricular foi a coordenação de ensaios clínicos, na área da neurologia, num centro de investigação clínica. No entanto, este foi um estágio muito rico e diversificado e portanto, eu também tive a oportunidade de desenvolver atividades em outras áreas do sector do medicamento, nomeadamente em farmacovigilância, escrita científica, gestão de dados e monitorização.

Este estágio representou o meu primeiro contacto com o mundo do trabalho e permitiu a criação de uma ponte entre o mundo académico e o mundo do trabalho. Este permitiu-me colocar em prática o conhecimento adquirido durante a Universidade, compreender como várias áreas do sector do medicamento funcionam na prática, complementar o meu conhecimento teórico e melhorar as minhas soft skills.

keywords Clinical Research Centre; Clinical Research; Clinical Trials; Coordination of Clinical Studies; Pharmacovigilance; Medical Writing

abstract

The present internship report aims to describe, in detail, my curricular training of ten months at the Unidade de Farmacologia Clínica of the Instituto de Medicina Molecular.

This training is part of the curricular activities of the second year of the Masters in Pharmaceutical Biomedicine of the University of Aveiro.

The main focus of this curricular training was the coordination of clinical trials, in the area of neurology, in a clinical research centre. However, this was a very rich and diversified training and therefore, I also had the opportunity of develop activities in other areas of the drug sector, namely pharmacovigilance, medical writing, data management and monitoring.

This training represented my first contact with the working world and enabled the establishment of a bridge between the academic world and the working world. It allowed me to put in practice the knowledge acquired during the University, to understand how various areas of the drug sector work in the practice, to complement my theoretical knowledge and to improve my soft skills.

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List of Abbreviations

ADR – Adverse Drug Reaction

ATC – Anatomical Therapeutic Chemical

CAML – Centro Académico de Medicina de Lisboa

CIC – Centro de Investigação Clínica

CIOMS – Council for International Organizations of Medical Sciences

CNPD – Comissão Nacional de Proteção de Dados

CRF – Case Report Form

CRO – Contract Research Organization

CT – Clinical Trial

CTA – Clinical Trial Application

ECG – Electrocardiogram

eCRF – Electronic Case Report Form

EMA – European Medicines Agency

EU – European Union

FAP – Familial Amyloid Polyneuropathy

FAQ – Frequently Asked Questions

FDA – Food and Drug Administration

GCP – Good Clinical Practices

GVP – Good Pharmacovigilance Practices

HD – Huntington's Disease

ICF – Informed Consent Form

ICH – International Conference on Harmonisation

ICSR – Individual Case Safety Report

IMI – Innovative Medicines Initiative

IMM – Instituto de Medicina Molecular

INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde I.P

ISF – Investigator Site File

IVRS – Interactive Voice Response System

IWRS – Interactive Web Response System

MAH – Marketing Authorisation Holder

MedDRA – Medical Dictionary for Regulatory Activities

NCA – National Competent Authority

OS – Observational Study

PD – Parkinson's Disease

PI – Principal Investigator

PSUR – Periodic Safety Update Report

R&D – Research and Development

SBM – Sub-unidade de Bioestatística e Metodologia

SC – Study Coordinator

SCV – Site Closure Visit

SDV – Source Data Verification

SIAHS – Syndrome of Inappropriate Antidiuretic Hormone Secretion

SIV – Site Initiation Visit

SNF – Sistema Nacional de Farmacovigilância

SmPC – Summary of Product Characteristics

SQV – Site Qualification Visit

SVIG – Portuguese Pharmacovigilance System Database

UFC – Unidade de Farmacologia clínica

UMC – Uppsala Monitoring Centre

URFLVT – Unidade Regional de Farmacovigilância de Lisboa e Vale do Tejo

WHO – World Health Organization

1. Introduction

This document is an internship report which aims to describe my curricular training of ten months carried out at the Unidade de Farmacologia Clínica (UFC; Clinical Pharmacology Unit) of the Instituto de Medicina Molecular (IMM).

The curricular training was carried out during the second year of my Master's Course in Pharmaceutical Biomedicine, provided by the University of Aveiro, and was undertaken in order to complete this course and acquire professional experience in clinical research, pharmacovigilance, medical writing and data management. It was supervised by Professor Doctor Joaquim Ferreira and Professor Doctor Alexandra Queirós.

The UFC is led by Professor Joaquim Ferreira and comprises six sub-units. During my training, I only developed activities in three of them: the Centro de Investigação Clínica (CIC; Clinical Research Centre); the sub-unidade de Bioestatística e Metodologia (SBM; Biostatistics and Methodological sub-unit) and the Unidade Regional de Farmacovigilância de Lisboa e Vale do Tejo (URFLVT; Regional Pharmacovigilance Unit of Lisboa and Vale do Tejo).

My curricular training started on 2nd September 2014 and lasted until 3rd July 2015. The training consisted of a rotating approach. I started my activities at the CIC and stayed there during two months, then I went to the SBM and developed activities there during two months and, subsequently, I went to the URFLV where I stayed during two months too. The last four months of my training were spent at the CIC. The rotating scheme of the training is represented in the Figure 1.

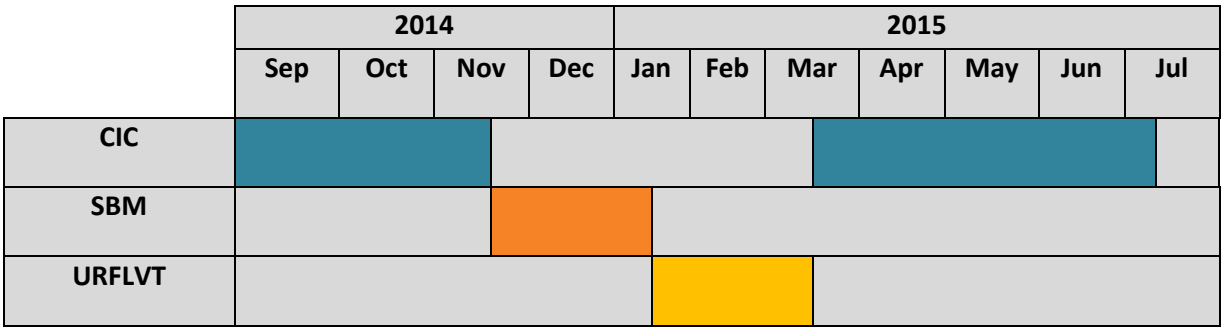

Figure 1 – Rotation Scheme of the Curricular Training

Throughout this report I am going to use the term "clinical studies" to define clinical trials (CT) and observational studies (OS). The term "drug" is going to be used too as "medicine" and "medicinal product".

1.1. Objectives

When I started the curricular training, in September 2014, I defined various objectives that reflected my expectations regarding the training and what I hoped to learn with it. The primary objectives were those that I necessarily had to achieve by the end of the training. The secondary objectives could be achieved or not by the end of the training.

1.1.1. Primary Objectives

- Acquire qualifications and skills in the coordinating of clinical studies;
- Perform all the activities that are within the competence of a Study Coordinator (SC);
- Understand how a Regional Pharmacovigilance Unit works, particularly the URFLVT, and perform the daily activities undertaken at the Unit;
- Apply the previously acquired academic background in a practical context and complement it;
- Acquire practical/professional experience in the drug sector and identify my areas of interest in this sector or related with the clinical research area;
- Improve my teamwork and communication skills and my capacity of interpersonal relationship.

1.1.2. Secondary Objectives

- Write a scientific paper related to the area of clinical research;
- Improve my writing skills by carrying out activities of medical writing;
- Understand how a Biostatistics and Methodological Unit works and acquire knowledge in this area by participating in the projects ongoing at the Unit;

1.2. Report Structure

This internship report is divided in seven main sections: Introduction – Chapter 1, Vision of Host Institution – Chapter 2, State of the Art – Chapter 3, On the Job Training – Chapter 4, Discussion – Chapter 5, Conclusion – Chapter 6 and References.

The first chapter, Introduction, describes the scope of this internship report, presents an overview of my curricular training and identifies the objectives that I hope to achieve at the end of the training.

The second one, Vision of Host Institution, presents an overview of the host institution, highlighting particularly the organization, constitution, objectives and activities developed by the UFC.

The State of the Art, the third chapter, provides some background on various topics of the drug sector that are essential to understand the scope of this report and the activities developed during the training.

The fourth chapter, On the Job Training, is the main chapter of this report. It describes all the activities that I carried out during my curricular training.

The fifth chapter, Discussion, presents a discussion about the ten months of training, highlighting the lessons learned during this time frame. The next chapter, Conclusion, sums up the final thoughts about the training.

The last section, References, lists all the references that I used to support this report.

2. Vision of Host Institution

The IMM was officially the host institution of my curricular training. More concretely, my curricular training took place at one of the 34 research labs of the IMM – the UFC. However, the UFC is not located in the building of the IMM but at the Centro Hospitalar Lisboa Norte, E.P.E. – Hospital Santa Maria (North Lisbon Hospital Centre, E.P.E – Santa Maria Hospital).

This section aims to present an overview of the host institution, highlighting the research lab where I developed my activities.

2.1. Instituto de Medicina Molecular

The IMM is a private and non-profit association created in December 2002. It is located on the campus of the Faculdade de Medicina da Universidade de Lisboa (Faculty of Medicine of the University of Lisbon) (1).

"The mission of the Instituto de Medicina Molecular (IMM) is to foster basic, clinical and translational biomedical research with the aim of contributing to a better understanding of disease mechanisms, developing novel predictive tests, improving diagnostics tools and developing new therapeutic approaches" (1, p.5).

The IMM is part of the consortium entitled Centro Académico de Medicina de Lisboa (CAML; Lisbon Medical Academic Centre) that comprises also the Faculdade de Medicina da Universidade de Lisboa and the Centro Hospitalar Lisboa Norte, E.P.E. – Hospital Santa Maria. The three institutions share the same University Campus (2).

2.2. Unidade de Farmacologia Clínica

The UFC was officially created on the 1st July 2013 and is one of the 34 research labs of the IMM. Currently comprises six sub-units: the CIC, the URFLVT, the SBM, the sub-unidade de Avaliação de Medicamentos e Revisões Sistemáticas (Drug Evaluation and Systematic Reviews sub-unit), the Outcomes sub-unit and the Pharmaco Magnetic Resonance Imaging sub-unit (1).

The main mission of the UFC is to contribute to the development of effective and safe therapeutic interventions through the establishment of optimized methodologies for the design, conduction, analysis and report of CT. The focus of the Unit is mainly on novel, early phase proof-of-principle clinical studies and new methodological and trial designs but the scope extends throughout the clinical development spectrum (1).

The UFC is located on the 3th floor of the Centro Hospitalar Lisboa Norte, E.P.E. – Hospital Santa Maria. However, the UFC operates in a physical space entitled Laboratório de Farmacologia Clínica e Terapêutica (Laboratory of Clinical Pharmacology and Therapeutics) which belongs to the Faculdade de Medicina da Universidade de Lisboa. The only sub-unit of the UFC which does not operate in this physical space is the CIC, which operates in a different floor of the hospital.

A description of the sub-units where I develop activities is presented below. Regarding the other three sub-units, I only provide a brief description since I did not develop any activity there and therefore I do not have much knowledge about these sub-units.

The sub-unit of Avaliação de Medicamentos e Revisões Sistemáticas comprises the Movement Disorders Cochrane Collaboration Review Group, which has expertise in conducting systematic reviews and related CT methodology issues (2).

The Outcomes sub-unit is focused on the study of measurement instruments, including biomarkers and patient-reported outcomes in drug evaluation (2).

The Pharmaco Magnetic Resonance Imaging sub-unit aims to detect micro-structural, functional and biochemical alterations in the central nervous system through the application of neuroimaging techniques (1).

2.3. Centro de Investigação Clínica

The clinical research centres, also known as sites, are a critical piece in the clinical development process (3). They are the entities responsible for conducting clinical studies, represent the physical space where the clinical studies are performed and are fitted with adequate human and material resources (3,4). Its ultimate purpose is to produce clean and reproducible clinical data in a timely and safe manner. The clinical research centres generate these clinical data by applying the study protocols on human subjects that they recruit. Through their activities, clinical research centres play a major role in moving investigational products through the clinical development phases on their way to regulatory submissions and ultimately, to market (3).

Clinical studies are becoming more complex and including more procedures per subject, therefore it is crucial that the team at the clinical research centre is aware of what it takes to perform good-quality clinical research in a timely, ethical and responsible way (3).

The CIC was established in 1999 and is located on the 6th floor of the Neurology Department of the Centro Hospitalar Lisboa Norte, E.P.E. – Hospital Santa Maria. Although the CIC uses the physical space of the hospital, it does not belong to the hospital. The CIC currently belongs to the UFC, being a sub-unit of it.

The centre has all the required conditions and equipment to conduct high quality clinical research. It has a meeting room where is possible to conduct all the necessary meetings and which is used by the study monitors who visit the centre to perform its monitoring activities. There is also another office room available to the SC. These two rooms together have enough space to archive almost all the documentation and laboratory material of the studies ongoing at the centre. The centre has also a consultation room to evaluate the patients and a room to collect biologic samples from the patients. Regarding equipment, both the meeting room and the office room have computers available with restricted access internet. The consultation room has all the medical calibrated material required to the assessments of the studies (e.g. sphygmomanometers, electrocardiographs, thermometers and scales). The CIC owns a calibrated centrifuge with temperature control to process patient samples.

In the CIC are conducted CT and OS in the field of neurology encompassing different diseases, namely: Parkinson's Disease (PD), Huntington's Disease (HD), Dystonia, Alzheimer's Disease, Multiple Sclerosis, Epilepsy, etc. The majority of the studies conducted until now at the CIC had as therapeutic indication the PD (38 CT; 4 OS) and Multiple Sclerosis (15 CT; 23 OS). The CIC also conducted a great number of studies in other diseases namely: Alzheimer's disease (16 CT), Epilepsy (13 CT; 1 OS); Familial Amyloid Polyneuropathy (FAP) (8 CT; 1 OS) and HD (4 CT; 1 OS). The Figure 2 illustrates all the clinical studies conducted at CIC since 1999 until 2015 distributed by therapeutic indication.

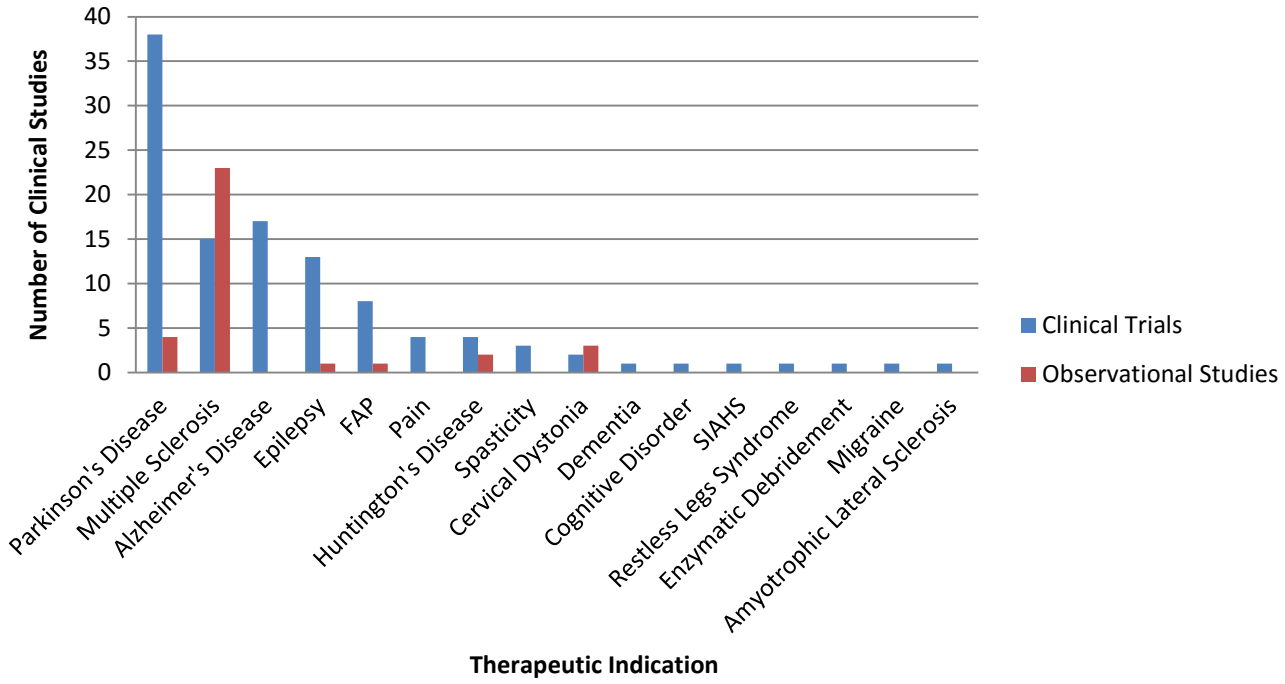

Figure 2 – Number of Clinical Studies Conducted at CIC by Therapeutic Indication (1999-2015) (SIAHS – Syndrome of Inappropriate Antidiuretic Hormone Secretion)

Figure 3 illustrates the total number of CT conducted at CIC distributed by phases since 1999 until 2015. The majority of the CT conducted at CIC was of phase III (69 CT) and of phase II (16 CT).

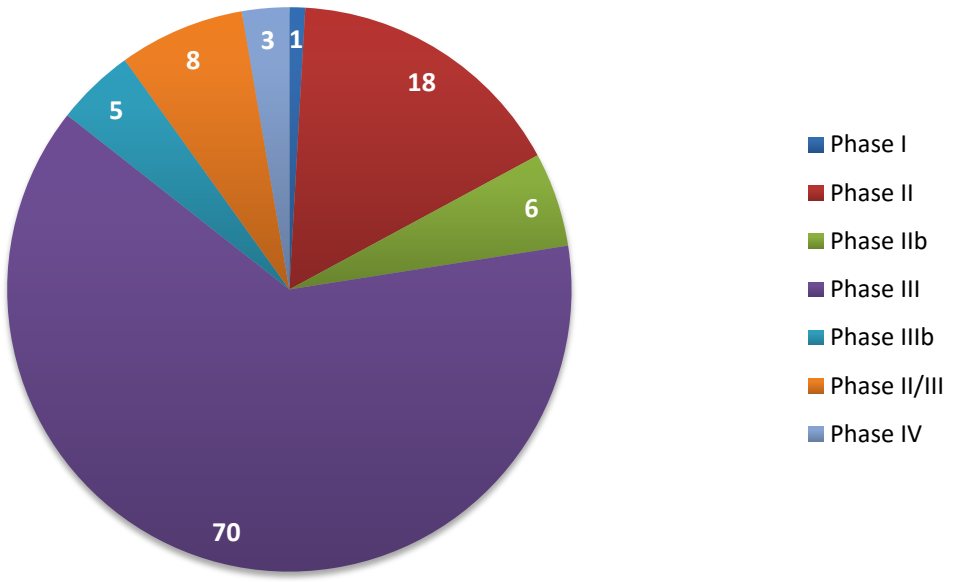

Figure 3 – Clinical Trials Conducted at CIC by Phase (1999-2015)

At the end of my training there were 22 CT and 10 OS on-going.

The information presented above resulted from a search done by me at the CIC. My search was based on questions to the team and in the consultation of an internal database with all the clinical studies conducted at the CIC since 1999 until 2015.

The CIC counts on a team of professionals qualified by education, training and experience. The team is highly motivated and willing to dispense time in the conduct of clinical studies. This is a great asset to the centre and the secret to being considered a centre of excellence.

The centre is comprised of a multidisciplinary team of health professionals which includes: SC, principal investigators (PI) and sub-investigators, a laboratory technician, nurses, pharmacists and psychologists.

The SC is usually considered the key element in the day-to-day activities of clinical research. The role played by the SC is essential to conduct CT with high quality and in a timely way. The responsibilities of a SC may include the following (3,5):

- participation in trial budget preparation;
- attend to investigator meetings;
- provide support in recruitment activities;
- data entry in Case Report Forms (CRF) and query resolution;
- archive and maintain the study files and records;
- transmission of study data (e.g., transmission of electrocardiogram (ECG) through telephone network);

- scheduling of patient visits and other procedures of the CT (e.g., some exams required by trial protocol);
- instructing the trial participants;
- coordinate with the pharmacist the preparation/dispense of the experimental medication;
- meeting with PI and study monitors;
- processing and shipping of biological samples to external laboratories;
- close out the CT.

The PI is the physician who is responsible for the conduct of a CT. The PI major responsibilities are first ensuring safety of trial participants; conducting the trial according to its protocol, the Good Clinical Practices (GCP) and applicable legislation and collaborating with the sponsor's team members (6). The PI is also responsible for the recruitment, enrollment, medical follow-up and withdrawal (if necessary) of trial participants, obtainment of the informed consent, prescription of the experimental medication, report of adverse events and serious adverse events and lastly delegation of trial tasks. The PI is always responsible for all trial activity and for all personnel performance, so he/she should choose their sub-investigators and coordinators carefully (7).

The sub-investigator is any member of the CT team designated and supervised by the investigator to perform critical trial-related procedures and/or to make important trial-related decisions (8).

The laboratory technician and study nurses are responsible for collecting biological samples. The study nurses can also give support in the administration of the experimental medication (e.g., when the experimental medication is administered through an infusion or injection).

The pharmacists are responsible for receiving, storing, dispensing and for the accounting of the experimental medication according to trial protocol.

The psychologists are essential in the neurology CT, since they administer several scales required by trials protocols to the trial participants and their caregivers (e.g., Mini Mental State Examination, Columbia Suicide Severity Rating Scale, etc).

2.4. Unidade Regional de Farmacovigilância de Lisboa e Vale do Tejo

The URFLVT is one of the four Regional Pharmacovigilance Units of the Sistema Nacional de Farmacovigilância (SNF; Portuguese Pharmacovigilance System) and covers the population encompassed by the Health Regional Administration of Lisboa and Vale do Tejo Region. The main purpose of the URFLVT is to receive, validate, classify, process and proceed to the causality assessment of spontaneous reports of adverse drug reactions (ADR) that occur in the area covered by the Unit, and lastly report them to Autoridade Nacional do Medicamento e Produtos de Saúde I.P (INFARMED, National Authority of Medicines and Health Products, IP).

The staff of the sub-unit consists of a physician which acts as director of the Unit and clinical coordinator; one pharmacist which acts as quality manager and pharmacist operating; one pharmacist which acts as pharmacist operating and pharmacist coordinator and one administrative assistant.

The SNF oversee the safety of the drugs commercialized in the national market, evaluating potential problems related with ADR and implementing safety measures whenever necessary (9).

In Portugal, the SNF was created in 1992. It was first established in a centralized manner, but it was realized quickly that its geographic decentralization, through the creation of various Regional Pharmacovigilance Units, would allow a positive proximity of the system to the health professionals and the involvement of the universities (10).

Currently, the SNF is comprised of the Direção de Gestão do Risco de Medicamentos (Medicine Risk Management Direction) of INFARMED, which coordinates the SNF, and by four Regional Pharmacovigilance Units: the Unidade Regional de Farmacovigilância do Norte (Northern Regional Pharmacovigilance Unit), the Unidade Regional de Farmacovigilância do Centro (Centre Regional Pharmacovigilance Unit), the Unidade Regional de Farmacovigilância de Lisboa e Vale do Tejo and the Unidade Regional de Farmacovigilâcia do Sul (Southern Regional Pharmacovigilance Unit) (9).

These Regional Pharmacovigilance Units cover the entire mainland Portugal and are responsible for assuring the proper collection, processing and evaluation of spontaneous reports of ADR and for promoting the continuous disclosure of the SNF and of the spontaneous reporting among potential reporters (health professionals, patients, students, etc.). Additionally, the Regional Units also carry out some pharmaco-epidemiological studies in the area of drug safety (10).

The Regional Pharmacovigilance Units are entities with technical and administrative autonomy and are headquartered in the various regions, usually in university institutions and/or research institutions in health. These carry out their activity within the defined legal framework and in close collaboration with the INFARMED, entity with which celebrate collaboration protocols or contracts for provision of services (11,12).

The Figure 4 shows the evolution and maturation of the SNF since their creation in 1992 until 2014. At the first years of existence of the SNF there was a high rate of underreporting. Over the years the reporting rate has been increasing reaching a total of 4618 ADR spontaneous reports in 2014, a trend that shows that the efforts of the Regional Pharmacovigilance Units to promote the SNF among health professionals were worth it (13). The graphic also shows the effect of the new pharmacovigilance legislation regarding the report of ADR by users. Since 2012 the report of ADR by users has been increasing and is expected to continue to increase over the next years.

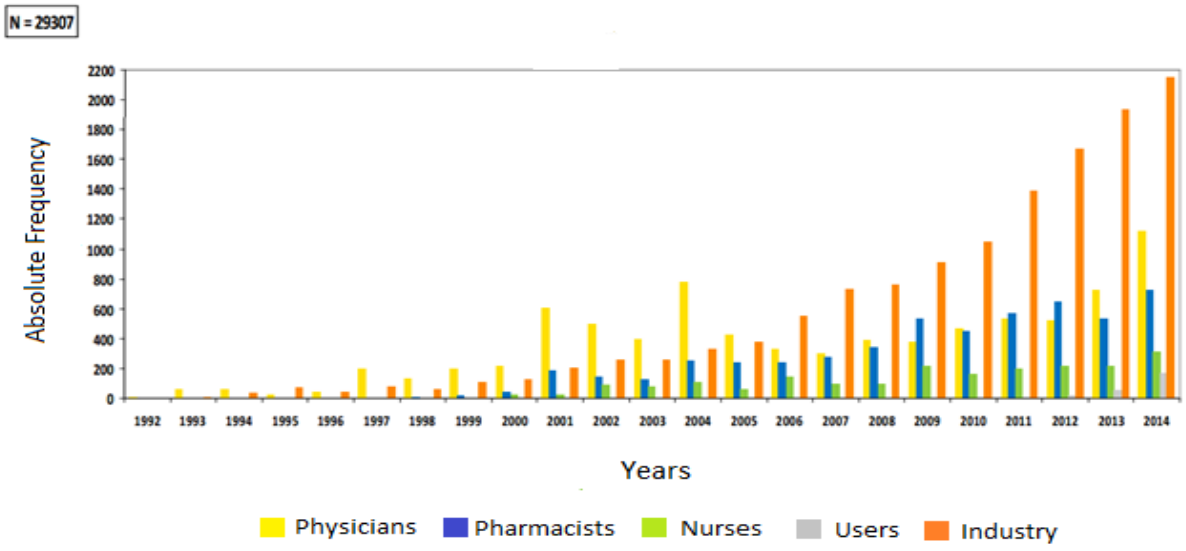

Figure 4 – Number of ADR Reports Received by the SNF by Reporter (1992-2014) (14)

2.5. Sub-Unidade de Bioestatística e Metodologia

This sub-unit plays activities of clinical data management; data quality control; biostatistics; medical writing and submission of scientific articles for publication in scientific journals; and development and submission of applications for scientific projects.

The sub-unit provides statistical support to all research projects, mainly related with design and analysis of CT and systematic reviews. Regarding the methodological support, the sub-unit aims to support in the design, conduct, analysis and reporting of clinical research studies and to optimize study design and feasibility (2).

The staff of the sub-unit consists of statisticians, data managers, project managers and physicians.

3. State of the Art

This section presents an overview of the drug development process focusing in the clinical development; the problems of the current research and development (R&D) model and new trends in the R&D of new drug products; the current status of the clinical research in Portugal; the Portuguese and European regulatory framework in the clinical research area as well as an overview of the pharmacovigilance including its role and history, the new European pharmacovigilance legislation and how medicines are supervised in Portugal.

3.1. Drug Development

The discovery of new medicines has been an important part of transforming many diseases over the years (15). The pharmaceutical industry has contributed to significant enhancements in patient well-being. Nowadays, the European citizens can expect to live up to 30 years longer than a century ago and with better quality of life. However, some diseases remain as major hurdles, namely Alzheimer's Disease, Multiple Sclerosis and orphan diseases (16).

Drug development is a stepwise process which includes drug discovery and laboratory development, preclinical studies, clinical development and regulatory registration, comprising a series of sequential discovery and development decisions (6,17).

A deeper understanding of the drug development process and of its steps helps to explain why so many compounds do not reach the approval phase (18).

3.1.1. Drug Discovery and Laboratory Development

The first step of the drug development process is entitled drug discovery. Drug discovery is driven by unmet medical needs and financial opportunity and focuses on understanding the disease, as thoroughly as possible, and on the identification of disease targets and potential therapeutic compounds (6).

Once a target has been identified, researchers conduct studies in cells, tissues and animal models to determine whether the target can be influenced by a drug (6,15).

Afterwards, researchers look for a lead compound, that is to say a promising molecule that could influence the target and, potentially, become a medicine. This is done in a variety of ways, including creating a molecule from scratch, using high-throughput screening techniques to select a few promising possibilities from among thousands of potential candidates, finding compounds from nature and using biotechnology to genetically engineer living systems to produce disease-fighting molecules (15).

Even at this early stage, researchers already are thinking about the finished product. Issues such as the formulation of a medicine and its delivery system (i.e. how the medicine will be administered) are critical to a compound becomes a successful new medicine in the future (15).

3.1.2. Preclinical Studies

The drug discovery phase whittles down thousands of compounds to a few hundred promising possibilities that are ready for preclinical testing (15). From a total of 5,000 to 10,000 compounds, only 250 reach the preclinical phase (19). In the preclinical phase, researchers conduct laboratory and animal studies to determine whether a compound is suitable for human testing (15). Before the start of any CT, results from preclinical studies or previous human studies should be sufficient to indicate that the drug is acceptably safe for the proposed investigation in humans (20). The purpose of these preclinical studies is to provide the information necessary to start the CT (6).

At the end of this phase, which can take several years, around five compounds move to the next stage of testing in humans. The pharmaceutical company files a CT Application (in Europe) or an Investigational New Drug Application (in United States of America) with the competent authorities to begin CT (15).

3.1.3. Clinical Development

Before describing the clinical development process it is important to define two concepts inherent to this phase: clinical research and CT.

According to National Institutes of Health, clinical research is defined as "research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Clinical research includes:

- Patient-oriented research: This type of research involves a particular person or group of people, or uses materials from humans. This research can include 1) mechanisms of human disease, 2) therapeutic interventions, 3) clinical trials, and 4) development of new technologies
- Epidemiological and behavioural studies: These types of studies examine the distribution of disease, the factors that affect health, and how people make health-related decisions.
- Outcomes and health services research: These studies seek to identify the most effective and most efficient interventions, treatments, and services" (21).

According to guideline "E6 – Good Clinical Practice" of the International Conference on Harmonisation (ICH), a CT is defined as "any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy" (8, p.3).

To obtain approval from a competent authority to market a new drug for use in humans, a series of CT must be conducted. These CT are performed throughout four phases: phase I, II, III and IV. Each phase has specific and different requirements for patient types, goals, inclusion/exclusion

criteria, design features and expected outcomes. Together, these trials build the dataset for safety and efficacy that hopefully will lead to product approval (6).

The time frame for these CT often is entitled clinical development and requires about 6 to 7 years (6). During the clinical development, a new drug is tested in human volunteers. Since this process involves both benefits and risks, pharmaceutical companies take great care to protect the safety of trial participants and to ensure that they are thoroughly informed about the trial and its potential risks so that they can provide informed consent to participate, as required by law. Pharmaceutical companies also guarantee that the trials are conducted correctly and with integrity and that trial results are disclosed at the appropriate time (15).

In the past, there were clear boundaries between the four fairly standardized phases of clinical drug development. However, the phases have become less well defined as questions previously addressed in one phase are being addressed in both earlier and later phases. In part, this new approach is designed to accelerate the acquisition of information required for approval and successful marketing of a new drug and for collection of full and sufficient safety information as early as possible (6).

Currently, CT can be classified according to when the trial occurs during clinical development (phase I, II, III or IV) or by their objectives (human pharmacology, therapeutic exploratory, therapeutic confirmatory and therapeutic use). "The phase of development provides an inadequate basis for classification of clinical trials because one type of trial may occur in several phases" and therefore a classification system based on trial objectives is a more realistic approach (20, p.5). Figure 5 illustrates the close but variable correlation between the phases of development and types of study by objective that may be carried out during the clinical development of a new drug. The shaded circles show the types of study most usually conducted in a certain phase of development, the open circles show certain types of study that may be conducted in that phase of development but are less usual (20).

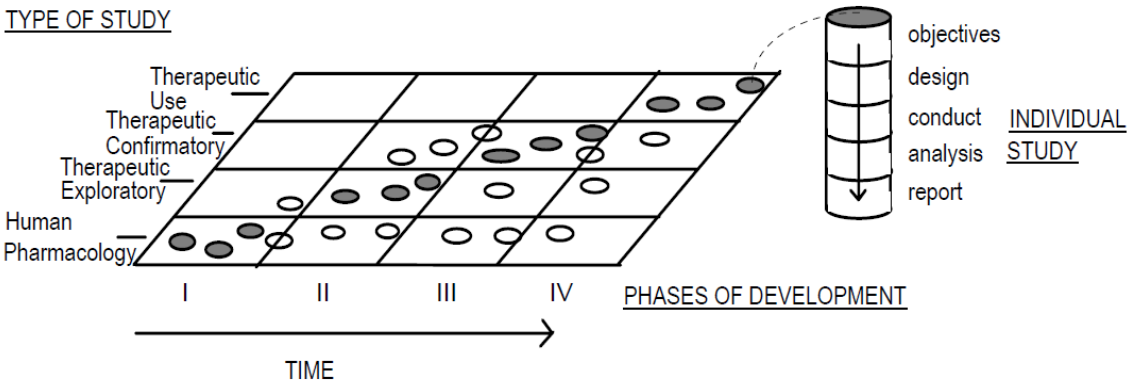

Figure 5 – Correlation between Clinical Development Phases and Types of Study (20)

A brief summary of each phase of clinical development is presented below.

Phase I (Most typical kind of study: Human Pharmacology)

Phase I studies are the first studies performed in human subjects (6). This phase starts with the initial administration of a new drug into humans (20). Sufficient preclinical information, including animal toxicology data, should be available to suggest that the new drug may be effective and safe in humans for the proposed indication (6).

Studies in this phase of development are usually conducted in healthy volunteers. However, there are circumstances in which healthy volunteers are not used. Typically, this happens when more "toxic" therapies are being tested, such as cancer chemotherapy and antivirals for the treatment of the human immunodeficiency virus. In these circumstances, patients with the disease are the first individuals to test the new therapy (6).

The objectives of this type of study are: to assess initial safety and tolerability; to define/describe pharmacokinetics and pharmacodynamics; to explore drug metabolism and drug interactions and to early estimate drug activity (20).

Phase II (Most typical kind of study: Therapeutic Exploratory)

Phase II studies are performed to determine the initial therapeutic efficacy of a drug in patients with the condition or disease of interest (6).

A characteristic of phase II studies is the use of relatively homogeneous populations due to narrow inclusion criteria. This feature increases the likelihood of identifying a positive effect and decreases confounding variables. On the contrary, the results obtained may not accurately reflect the effectiveness of the drug in the more typical heterogeneous population. Phase II studies are therefore well controlled and closely monitored (6).

The primary phase II studies are dose ranging studies and are designed to provide proof of principle. A major focus is to find the appropriate dose(s) and regimen for the larger studies required in phase III (6,20).

Several products fail at this phase and are "killed", which is desirable and necessary before moving ahead to the very expensive and labour intensive phase III study program (6).

Phase III (Most typical kind of study: Therapeutic Confirmatory)

Phase III studies are design to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and target population (20). These studies should provide an adequate basis for marketing approval, allowing extrapolation to the general population (6,20).

The decision to move ahead with phase III studies is a major one because the costs are considerably higher than for the two earlier phases together (6).

Submission of a Common Technical Document or New Drug Application requires at least two well-designed phase 3 studies that demonstrate both efficacy and safety in a large number of patients with the target disease (6).

Phase IV (Variety of studies: Therapeutic Use)

Research on a new drug does not end when the discovery and development phases are completed and the product is on the market. Instead, pharmaceutical companies carry out extensive post-approval research to monitor safety and long-term side effects in patients using the medicine. The competent authorities require that pharmaceutical companies monitor a medicine for as long as it stays on the market and submit periodic reports on safety issues. Pharmaceutical companies must report any adverse events that happen from use of the medicine (15).

Phase IV studies are performed after a new drug obtains marketing approval. This type of studies serves multiple purposes and comprises many different kinds. In general, characteristics of phase 4 studies are that they can be very large and have a more simple study design. Even though these studies were not considered essential for initial approval, they provide additional data that could change the prescribing information or the use of the drug (6).

This research phase is essential to improving researchers' and clinicians' understanding of medicine's potential uses and its full benefits for health and quality of life (15).

3.1.4. Regulatory Registration

If the results of all three CT phases indicate that the new medicine is safe and effective, the sponsoring company submits a Common Technical Document (in Europe) and/or a New Drug Application (in United States of America) to the competent authorities. These applications are a request for competent authorities approval to market the new medicine and contain the results and data analysis from the entire CT program as well as the earlier preclinical testing. It also comprises proposals for manufacturing and labelling the new medicine (15,18).

Scientists at competent authorities carefully review all the data from all of the studies on the medicine and, after weighing the benefits and risks of the potential medicine decide whether to grant approval (15).

3.2. Current R&D Model and New Trends

Designed in the early 1960s, the model for pharmaceutical innovation, which is represented in the Figure 6, has remained practically unchanged for nearly 50 years. During a period when most other research-based industries have made frequent modifications to their R&D process, the pharmaceutical industry continues to utilize a drug development process that is complex, inefficient, risky, expensive and time consuming (22).

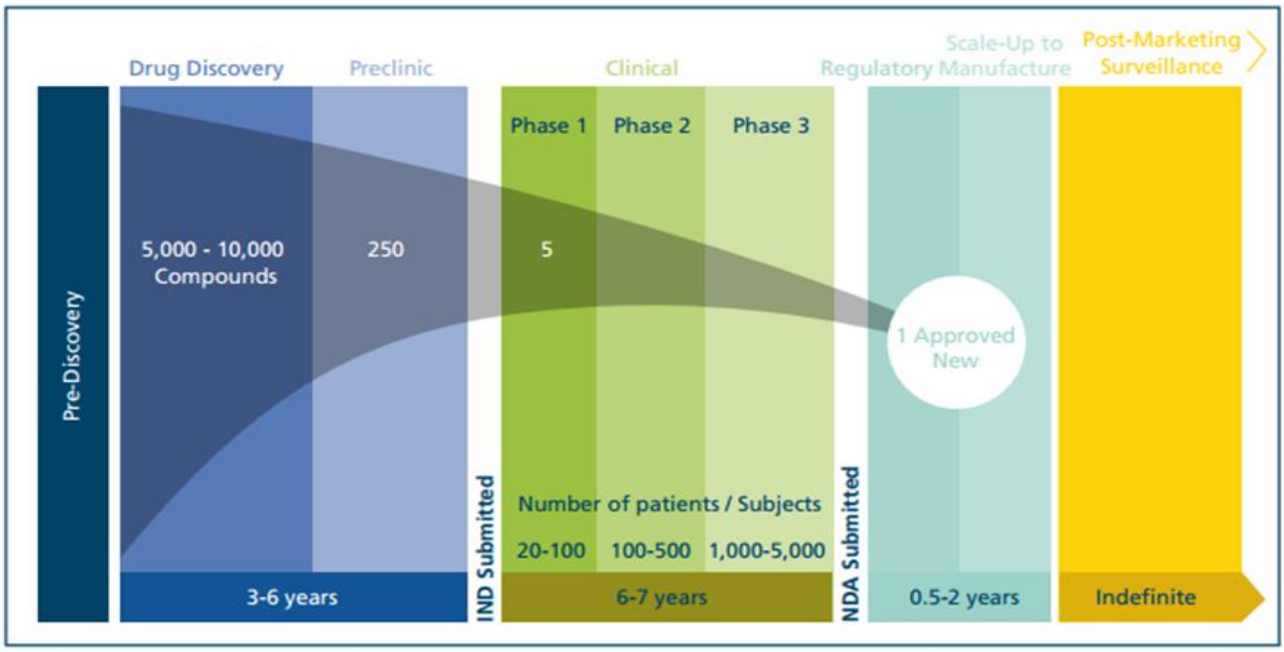

Figure 6 – Current Drug Development Process (23)

On average, it takes about 10 to 15 years for a new drug to complete the journey from initial discovery to the market (15). The time for exclusivity of product manufacturing and sales by the drug's originator company is often short after product approval. The majority of drug patents have only about 5 years left after product approval, although a patent exists for 20 years. This situation relates to patenting of a drug during the early research stage and the long time frame for R&D, which uses up the patent life before approval (6).

High attrition rates are another major challenge for pharmaceutical industry (22). Of every 5,000 to 10,000 compounds synthesized, on average, only 5 are tested in CT and only one of these is approved (6). The medicines that reach CT have a chance of less than 12% of being approved (18).

Additionally, there are other constraints, namely the reimbursement environment is increasingly restrictive; a large number of top-selling products are losing their patents and the regulatory environment has become extremely restrictive and much more risk averse (24).

Long development times coupled with very low success rates translate into high overall R&D costs for the pharmaceutical industry (22). The average R&D investment for each new medicine is $2.6 billion, including the cost of failures (18). Clinical spending rises as we proceed from phase I to III, directly related to the size of the CT and their greater diagnostic and monitoring complexity (6).

The biopharmaceutical industry is continually adapting to produce innovative treatments more efficiently (15). Biopharmaceutical companies are re-examining old and inefficient models of R&D and embracing new approaches to improve productivity and performance. In particular, biopharmaceutical companies are increasing their utilization of global outsourcing, expanding their use of information technologies in CT protocols and patient recruitment, and speeding the adoption of improved clinical study designs, including adaptive CT. Most importantly, many

biopharmaceutical companies are reassessing their focus on R&D strategies that emphasized broad diseases areas with large potential for sales, or blockbuster drug development strategies, and instead are favouring those that address smaller patient populations, specialized care, and unmet medical needs (25). To address the most complex scientific and technological challenges, partnerships and collaborations are becoming increasingly common among researchers from biopharmaceutical companies, academic medical research centres, non-profit organizations, patient advocacy groups, and others. In working together to address these challenges, partners share risks and are able to exchange intellectual, financial, and in-kind resources (18). Precompetitive partnerships, which seek to advance basic research, are a growing part of this approach (15). An example of these partnerships is the European Union's (EU) Innovative Medicines Initiative (IMI), a public-private partnership launched in 2008 between the European pharmaceutical industry, represented by the Federation of Pharmaceutical Industries and Associations, and the EU, represented by the European Commission. The IMI aims to improve health by speeding up the development of, and patient access to, innovative medicines, particularly in areas of unmet or social need. It does this by facilitating collaboration between the key players involved in healthcare research: academic institutions, pharmaceutical companies and other industries, small and medium-sized enterprises, patient organisations and regulatory authorities (26).

The majority of the biopharmaceutical companies now acknowledge that small incremental enhancements in R&D efficiency may not be sufficient. It is necessary a transformational overhaul of the R&D paradigm (25).

3.3. Clinical Research in Portugal

The pharmaceutical industry is increasingly selective regarding the locations to conduct their CT, giving priority to countries offering better conditions. Portugal is not among these countries and has been losing its competitiveness progressively (19).

The differences in the transposition of the EU CT Directive by the various Member States were already recognized as one of the main factors of loss of efficiency in the EU and inequality between Member States (19).

According to information available on the database clinicaltrials.gov only 1,216 of the 54,440 clinical studies conducted in Europe, between 2000 and April 2015, were carried out in Portugal. The Belgium, a country with a number of inhabitants similar to Portugal, conducted 6,020 of the 54,440 clinical studies in the same time frame. These data evidence that Portugal is still far away from the European reality (27).

The number of CT submitted in Portugal between 2006 and 2014 decreased 21%, from 160 to 127 studies. 2011 was the year with lowest number of CT submitted since 2006 until 2014, with only 88 trials.

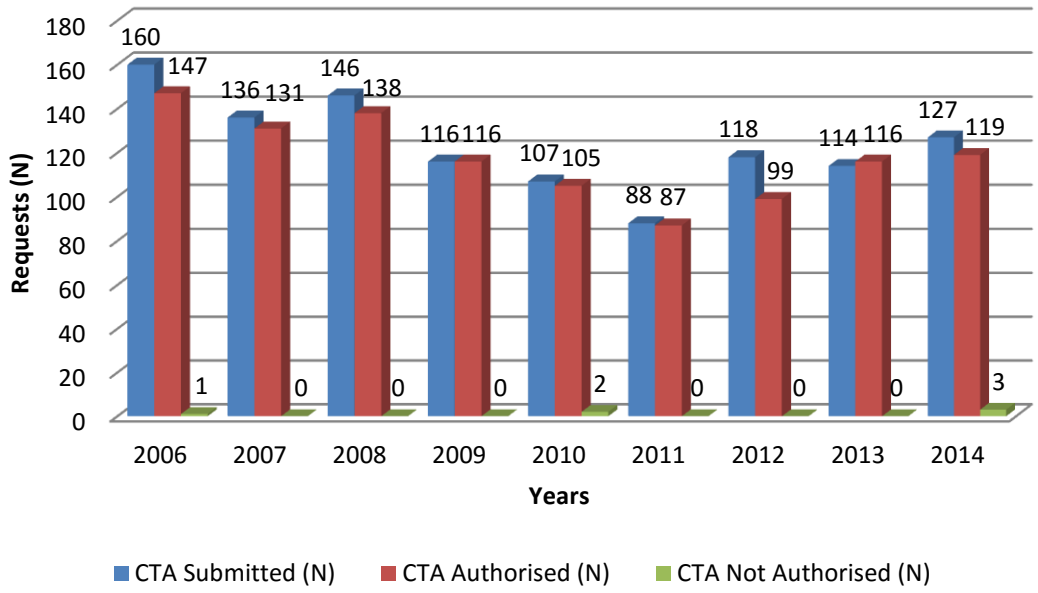

Figure 7 – Number of CTA Submitted, Authorised and Not Authorised in Portugal by Year (2006-2014) adapted from INFARMED Website (28)
(CTA – Clinical Trial Application)

Portugal has also a very low recruitment rate compared with other countries with a similar number of inhabitants, such as Belgium and Czech Republic. The low number of patients enrolled in Portugal is the result of several factors, namely the reduced number of sites that participate in each trial conducted at our country in comparison with other countries that have more sites conducting the same trial. Moreover, the ability of the Portuguese sites to recruit patients is clearly lower than the ability of other countries, and often falls short of the planned (19).

The majority of the CT submitted in 2014 were phase III (81%). On the contrary, only 10% of the CT submitted in 2014 were phase I. The number of phase II CT submitted between 2006 and 2014 has not varied much (20% in 2006 and 24% in 2014). However, there were a reduction in the number of phase III and IV CT submitted (phase III: 104% in 2006 and 81% in 2014; phase IV: 27% in 2006 and 12% in 2014) and an increase in the number of phase I CT submitted between 2006 and 2014 (2% in 2006 and 10% in 2014) (28).

The therapeutic areas with more CT authorized in Portugal, by year, are oncology, nervous system and infectious diseases. Together, these therapeutic areas represent more than half the number of trial authorized (28).

Despite these scenario, in 2012 the pharmaceutical industry invested 36 million euros in clinical research in Portugal, which contributed to a saving in the public expense of 3,5 million euros. The CT activity was responsible for a Gross Value Added of 72 million euros in 2012 and for each euro that is invested in clinical research, it is estimated that there is a return of 1.98 euros for the Portuguese economy. The clinical research is one of the activities with the highest return of investment of the country (19).

The national regulatory framework for the conduction of CT is currently governed by the Law 21/2014 of April 16th, which transposes the EU Directive 2001/20/CE, April 4th. The Law 21/2014 of April 16th aims to contribute to the promotion of clinical research in Portugal and to increase the competitiveness and transparency in this sector (29).

The entry into force of this law has overcome some of the major constraints of the clinical research area in our country as shown in Table 1. (19)

Table 1 – Comparison Between the Clinical Research Framework in Portugal Before and After the Law 21/2014 of April 16th (4,19)

Before	After
Uncompetitive deadlines for approval of CT Average time for approval of a CT in Portugal = more than 70 days	Opinion of the ethics committee within not more than 30 days Authorization of the INFARMED and CNPD within not more than 30 days
Mandatory approval of CT by the Comissão Nacional de Proteção de Dados (CNPD; National Committee of Data Protection) without legally defined deadlines	
Absence of legal deadlines for approval of the CT financial contract	Approval of the financial contract within not more than 15 days
Lack of a platform to promote and support the clinical research	Creation of the Registo Nacional de Estudos Clínicos (National Register of Clinical Studies)

3.4. Regulatory Framework

Any health professional working in the clinical research area needs to deal with and respect the applicable ethical, legal and regulatory requirements (5). A brief description of the main guidelines and laws in the clinical research area is presented below.

The ICH-GCP E6 guideline "is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible." (8, p.1) This guideline sets forth a tripartite standard for the conduct of CT among the United States, EU, and Japan (17).

The Declaration of Helsinki is a statement of ethical principles for medical research involving human subjects and was first developed in 1964 by the World Medical Association. This Declaration has undergone several subsequent revisions over the years; the last one was in 2013 (5,30).

The Directive 2001/20/CE, April 4th (31), also known as the EU CT Directive, establishes the requirements for the conduct of CT of experimental drugs in the EU. This directive was first

transposed into the Portuguese law by the Law 46/2004 of August 19th (32). The Law 46/2004 was repealed by the Law 21/2014 of April 16th (4), in force since June 2014.

The Directive 2005/28/CE, April 8th (33), also known as the EU GCP Directive, lays down the principles and detailed guidelines for GCP in CT of experimental drugs in Europe (34). This directive was transposed into the Portuguese law by the Decree-Law 102/2007 of April 2nd (35).

The Directive 95/46/CE, October 24th (36), concerns the protection of subjects personal data and the free movement of such data. This directive was transposed into the Portuguese law by the Law 67/98 of October 26th (37).

3.5. The Role of Pharmacovigilance

Pharmacovigilance refers to the science and activities related with the detection, assessment, understanding and prevention of ADR and other problems linked to drugs (10). It has a crucial role in protecting Public Health through the ongoing evaluation of the risks and benefits of drugs, being a key tool in the monitoring and guarantee of drug safety (11).

Indeed, the drugs are neither harmless nor absolutely safe and therefore its use may cause, in certain circumstances and in some of its users, ADR (12).

The ADR represent an important Public Health problem since they result in high rates of mortality and morbidity, entailing consequently great costs for health systems. A study developed in 1998 in the United States by Lazarou, et al. estimated that ADRs are between the 4th-6th cause of death (10).

The CT performed to support the granting of a marketing authorization to a medicine have several limitations as regards the identification of possible ADR, namely: reduced number of subjects exposed to the experimental medication; restricted inclusion criteria that exclude subjects with associated pathologies and that take concomitant medications and the tendency to not include population groups such as the elderly, children and pregnant women. Additionally, certain events of lower incidence or which occur over the long term are difficult to detect during the CT since they are limited in time. Thus, the safety profile of a medicine is largely unknown when the marketing authorization is granted (10,11).

“No drug which is phamacologically effective is entirely without hazard. The hazard may be insignificant or may be acceptable in relation to the drug’s therapeutic action. Furthermore, not all hazards can be known before a drug is market; neither tests in animals nor clinical trials in patients will always reveal all the possible side effects of a drug. These may only be known when the drug has been administered to large number of patients over considerable periods of time (11, p.22).” (Committee on Safety of Drugs, U.K.; 1969/1970)

The phase after the granting of the marketing authorization of a medicine is of great importance for the detection of ADR, since the medicine is used in a real context and in a widened and heterogeneous population. Indeed, the majority of the ADR occur in this phase (10). The awareness that the pre-marketing CT do not allow an adequate knowledge of drug safety due to

methodological reasons resulted in the creation of structures to monitor the drug safety during their marketing (38).

The creation of Pharmacovigilance Systems worldwide began to appear in the 1960s, after the knowledge by the community of the Thalidomide Tragedy. This disaster was caused by the administration to pregnant women of thalidomide, a drug promoted for use by this specific population, which resulted in thousands of cases of phocomelia in children exposed to this unsafe drug during the gestation period. Due to the inexistence of systems to monitor drug safety after their marketing authorization, it was necessary four years (from 1957 to 1961) to identify the teratogenic effects of thalidomide, despite the emergence of many thousands cases of phocomelia at that time (10,39).

The Thalidomide Tragedy was first discussed in 1961, highlighting the need to constant drug surveillance after their marketing. Thus, during the Sixteenth World Health Assembly, in 1963, it was decided to implement the global monitoring of ADR, aiming the detection, recording and evaluation of ADRs, in order to minimize the risk associated with the use of drugs (10).

Thereby, it was developed in 1968 a pilot project of international research and monitoring, coordinated by the World Health Organization (WHO), which aimed to create an International Pharmacovigilance System. This system aimed to develop the ADR detection system, called WHO Programme for International Drug Monitoring, and was initially composed of the following countries: United Kingdom, United States of America, Federal Republic of Germany, Canada, Netherlands, Ireland, Sweden, New Zealand, Australia and Czechoslovakia, which created the respective National Centres of Pharmacovigilance (10,39).

The program is coordinated since 1978 by the Uppsala Monitoring Centre (UMC) in Uppsala, Sweden. In this centre are collected, processed and stored the spontaneous reports of all member states and is also from here that are issued warnings, related with potential safety problems, to the regulatory authorities of each member country (10).

Each country has currently its own monitoring systems of marketed drugs. To sum up, the pilot project, created in the 60s, led to the development of different national pharmacovigilance systems that still exist all over the world (10). The Portuguese Pharmacovigilance System is an example of those systems.

The drug surveillance carried out by the Portuguese Pharmacovigilance System is based mainly on spontaneous reporting of ADR made by health professionals or any ordinary citizen to the National Competent Authority (NCA) (10).

"A spontaneous report is an unsolicited communication by a healthcare professional, or consumer to a competent authority, marketing authorisation holder or other organisation (e.g. Regional Pharmacovigilance Centre, Poison Control Centre) that describes one or more suspected adverse reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organised data collection systems where adverse events reporting is actively sought." (40, p.8)

The reports are submitted in writing, using the paper reporting forms, and are sent by post or fax or can be communicated by telephone or e-mail to the NCA. The report can also be done through the filling of the online reporting form on the ADR Portal (Portal RAM) (10,38).

Should be reported to the NCA all suspected serious ADR, even if they are already described in the summary of product characteristics (SmPC); all suspected ADR not described in the SmPC, regardless of the seriousness, and all suspected of increase in the frequency of ADR (serious and non-serious) (12).

The spontaneous reporting systems have many advantages, namely: cover all the medicines available on the market and its entire life cycle; are cost-effective methods; encompass the entire consumer population of medicines; do not interfere with the prescription habits and allow the identification of rare ADR (38). Notwithstanding all these advantages, the main value of the spontaneous reporting systems lies in early detection of possible drug safety problems that have gone unnoticed until then (11,41).

However, these systems have as a major limitation the underreporting of suspected ADR. In other words, the underreporting means that the cases spontaneously reported to the NCA only represent a small portion of the number that has truly occurred (10,41,42). The underreporting of suspected ADR limits the risk assessment of medicines and delays the generation of risk signals (10). It is also important to highlight that underreporting does not only affect older drugs and non-serious ADR. New drugs and serious ADR also suffer from underreporting (41).

For a spontaneous reporting system to be effective, it is essential the active participation of their reporters and therefore the underreporting of ADR remains as a key problem in all countries (39).

Spontaneous reporting systems should be seen as generators of hypotheses that often need to be further investigated by other methods, such as pharmacoepidemiological studies, especially in order to confirm and quantify the risk (11).

In an attempt to facilitate spontaneous reporting in Portugal, the INFARMED (the Portuguese NCA) developed the ADR Portal. This is a tool for online ADR reporting where health professionals and patients can report ADR by filling out an online reporting form (43).

Additionally to the ADR report submission, the ADR Portal also contains pharmacovigilance information, news and useful links. In the ADR Portal the citizens can also found a Frequently Asked Questions (FAQ) section and objectives, definitions and contact details within the scope of pharmacovigilance (43).

The ADR Portal comprises internal management features which allow the communication and information management between the Regional Pharmacovigilance Units and the INFARMED, the system's coordinator. Reports submitted into the ADR Portal become automatically available for the corresponding Regional Pharmacovigilance Unit and are subsequently validated and processed on the Portal's platform by their staff. Then, they are uploaded into the Portuguese Pharmacovigilance System Database (SVIG) and after the handling by the pharmacovigilance team

of the INFARMED are made available for electronic transmission to the EudraVigilance and VigiBase databases (43).

In 2004, it was created by the INFARMED the national database named SVIG for the registration of ADR reported to the SNF. In this database are introduced the reports of suspected ADR that occurred in Portugal and sent by:

- the various Regional Pharmacovigilance Units of the mainland Portugal;
- health professionals or citizens of the autonomous regions (Madeira and Azores), that report directly to INFARMED;
- the pharmaceutical industry – Marketing Authorisation Holders (MAH) (12).

The SNF is connected with the VigiBase, the WHO global database created in 1968 that receives the reports of ADR from member countries. The VigiBase is updated on a continuous basis with new Individual Case Safety Reports (ICSR) and it is developed and maintained by the UMC on behalf of the WHO. By May 2015 this database contained over 11 million ICSR (12,44).

The SNF is also connected with the European Medicines Agency (EMA) database, the Eudravigilance Data Base Management System, created in December 2001. It is a centralized European database of suspected ADR that occurred with the utilization of medicines that are marketed or being studied in CT in the European Economic Area (12,45).

In July 2012 the new European pharmacovigilance legislation, which comprises the Directive 2010/84/EU and the Regulation (EU) No 1235/2010, come into effect. This legislation amended the existing pharmacovigilance laws contained in Directive 2001/83/EC and Regulation (EC) No. 726/2004 (46).

The implementation of the new pharmacovigilance legislation has brought new responsibilities for regulators and the pharmaceutical industry in the EU (47).

Since July 2012, all individual European citizens can report their suspicions of ADR directly to the NCA, without having to report them first to a health professional (10,47).

It is also required the creation of national web portals of medicines connected with the European portal, in order to allow disclose relevant information to the community in general. This relevant information includes SmPC, package leaflets, reports assessment, summaries of risk management plans as well as the different ways of reporting suspected ADR to the NCA by the citizens (health professionals, patients, etc.), including the online notification (12).

The definition of ADR has also changed and become more comprehensive, including now not only the noxious and unintended effects resulting from the use of medicinal products within the terms of the marketing authorization but also outside including overdose, off-label use, misuse, abuse and medication errors and occupational exposure (12,40).

4. On the Job Training

This section provides a full description of all the activities that I carried out during the ten months of curricular training in each of the sub-units of the UFC: the CIC, the SBM and the URFLVT. Firstly, I am going to describe the activities that I developed in the CIC, then the activities developed in the SBM and lastly the activities developed in the URFLVT.

4.1. Centro de Investigação Clínica

My internship at CIC was divided in two parts, as previously mentioned. The first part started on September 2nd and lasted until 10th November. The second part started on 13th March and lasted until 3rd July.

In my first two weeks at CIC I met the team that collaborates in the conduction of the clinical studies, I got to know the physical space of the centre and understood how it was organized, I read the protocols of each clinical study that was being conducted at the centre, I became familiar with the documents and laboratory material of each clinical study and I learned how to process laboratory samples. I also received the necessary training, given by the two senior SC who work at the CIC, to perform all the activities of a SC.

A SC can take over a great number of responsibilities and activities. Throughout this sub-section I am going to describe all the activities that I carried out as SC and some other activities that I did not carry out but that I consider to be important to understand how a CT is implemented, conducted and completed.

Study Visits

The trial site visits conducted by the sponsor/Contract Research Organization (CRO) can be divided into four categories: Site Qualification Visit (SQV), Site Initiation Visit (SIV), Interim Monitoring Visits and Site Closure Visit (SCV) (48). The feasibility phase can be considered a pre-CT phase in which the interest of the investigators to conduct the trial and the conditions of the site are assessed by the sponsor/CRO.

The subjects trial visits at the centre can be divided in the following visits: screening visit, baseline visit, regular visits, unscheduled visits (if necessary), final visit and post-study follow-up visit(s).

Feasibility Phase (Investigator/Site Selection)

The selection of the investigators and sites for the conduction of a trial is a critical issue. Shortly, to do this selection is necessary to evaluate three criteria: qualification, recruitment potential and relationship needs (5).

The investigators and the sites must be qualified. They must have the proper experience in the therapeutic indication studied in the trial, trained staff, proper facilities and other pertinent qualifications specific for each trial. The site must also have access to the patients, either from their own practice or from referrals. The last criterion is relationship needs, since typically there are sites that are of importance because of relationships or strategic importance (5).

In the feasibility phase the sponsor/CRO contacts the PI of their interest to assess the interest and capacities of these PI/sites to conduct the trial. Generally this contact is done along with the sending of a feasibility questionnaire to the PI of interest in order to evaluate and select the most suitable PI/sites. This questionnaire basically consists of several questions about the conditions of the site (facilities, material, human resources, and clinical research experience), the experience of the PI and the number of patients that the PI expects to recruit. The feasibility questionnaire is completed by the PI with the support of the SC and then is sent back to the sponsor/CRO. After this process, the PI waits for feedback.

Site Qualification Visit

The next step after the feasibility phase is the conduction of a qualification visit.

The SQV consists of a visit of the sponsor/CRO to the site in order to asses if the PI/site truly meets all the requirements for the conduction of the trial. This visit is done by the study monitor of the trial, which meets with the PI and SC. In the SQV the PI signs the confidentiality agreement and the study protocol is presented and discussed. In this visit, other issues are discussed, namely: the number of patients that should be recruit and the financial contract.

The SQV can be very different according to the experience that the sponsor/CRO has with the site. If it is the first time that the sponsor/CRO visits the site, usually the SQV lasts longer. If the sponsor/CRO already had a past experience with the site, the SQV can be quicker or can be even by telephone.

After this phase, the site is contacted by the sponsor/CRO to be informed whether it was selected or not.

Investigator Meeting

When all of the investigators and the sites are selected to participate in a CT, the sponsor or CRO responsible for the trial will hold an Investigator Meeting (49).

Representatives from each site, generally the PI and SC, will participate in the meeting together with representatives from the sponsor's clinical team, regulatory affairs, data management and quality assurance departments. (49).

The Investigator Meetings can be considered as a training session for the participants. At the final of this type of meeting, the participants should understand completely the protocol and how to conduct the CT. This is also an excellent opportunity for the investigators and their staffs to ask questions about the trial and trial conduct (49).

During my training I did not participate or provided support to any feasibility process, SQV or Investigator Meeting, but everything about these processes was explained to me by the seniors SC. I did not attend to any SQV because no SQV took place during my internship at CIC and regarding the Investigator Meetings, only the senior SC at the CIC were authorised to attend.

Site Initiation Visit

Before the start of trial enrollment at the site, a SIV is conducted (48). This visit is characterised by the implementation of the CT in the site and after the SIV, the site is considered officially started and subject recruitment can begin (49).

The study monitor will schedule the SIV with the PI and SC by phone or e-mail and will send a follow-up letter in writing in order to confirm the date and time of the visit and the staff's availability for the visit. All study staff participating in the trial should be present in this important visit (49).

For site initiation, the site must submit the required regulatory documents, have the protocol and the Informed Consent Form (ICF) approved by the Institutional Review Board, have a contract with the sponsor, and have all other issues in order if applicable, namely the validation of sample shipping and training on Electronic Data Capture (5).

During this visit, the monitor will review in detail the protocol (design of the trial, inclusion and exclusion criteria, experimental drug, etc.); the ICF; the experimental drug dispensation and accountability; the adverse experience and serious adverse experience reporting; the CRF completion; the PI and staff responsibilities (delegation log); the regulatory documents and source documentation and will answer any question that the site may have (5,49).

The SIV is also a training meeting. It is the last training on the protocol that the investigators and their staff will have before beginning to recruit and enroll subjects in the trial (49).

I had the opportunity to attend to a SIV during my internship at CIC.

Screening Visit

Before carrying out the screening visit, the potential trial participants are approached in order to assess their interest in participate in the clinical study. They can be approached in a routine visit to the hospital by the study investigator; contacted by phone or referenced by physicians of other hospitals or health centres.

After this first contact, a visit is scheduled to give more information about the study, discuss this information with the patient and clarify any doubts the patient may have. If the patient accepts to participate in the clinical study, an ICF is signed and dated by the patient and the investigator and then a screening visit is conducted. The ICF must always be signed before carrying out any procedure of the trial and a copy of this document must be given to the patient.

The screening visit allows to determine which of the potential trial participants can actually be included in the study.

During this visit the SC helps the investigator with any doubt about the ICF, protocol and amendments to these documents. The SC also informs the patients about the logistics of the procedures to be conducted in the screening period (e.g., an ophthalmological exam) and highlights their availability in helping them with any situation related to the CT (e.g., if the patient

does not feel well he/she can contact the SC). The SC also gives support, if necessary, to the rest of the team such as psychologists, nurses, laboratory technicians, among others.

The screening period is the time available to conduct the screening exams/tests and for the laboratory determine the eligibility criteria. This period of time exists because of the logistics of performing the procedures necessary to include the trial participants (e.g., if a trial needs a genetic confirmation of the disease of interest as part of the inclusion criteria, then the time spent waiting for the central laboratory results is part of the screening period) (5).

The SC has the role of scheduling the exams/tests required for the trial and provides this information to the patients. Whenever necessary, the SC also organizes the transport of the patients.

If a patient meets all the inclusion criteria it is included in the study and a baseline/randomization visit is scheduled.

I provided support in several screening visits of different studies.

Screen Failure

In all CT some potential trial participants will fail to pass the screening criteria. When this situation happens, the study subject is considered a “screen failure” since he/she does not meet one or more criteria required for participation in the clinical study and therefore cannot be included in it (50,51).

It is important to document the reasons for screen failures in any CT. This record provides information in relation to the feasibility of recruiting study subjects from each site and may justified and result in protocol modifications based on frequency of screen failures when the motive for screen failures is common among the study population of interest. Additionally, some trial protocols allow rescreening of potential trial participants after a certain time interval (50).

To be eligible to participate in a CT, a patient must meet all of the inclusion criteria and none of the exclusion criteria (52).

Determining appropriately the study eligibility is as important as the informed consent process. The sponsor/CRO, ethics committee and competent authorities always review these two processes because they direct affect the health and safety of the study subjects (52).

During my training I conducted some screening visits that resulted in screen failures. It is always complicated to the team when this happens since a participant is lost, the effort of the team to include the patient is wasted and a patient lost an opportunity to try an innovative medication for his/her disease. Besides this, it is never easy to communicate to the patient or their relatives that he/she cannot be included in the trial despite his/her will.

Baseline Visit

The baseline visit is carried out at or very close to the time when the subjects are randomized to trial treatment/intervention (53).

This is a critical visit as all observations recorded at this visit will be the basis for comparison with all observations made while on the study treatment. Therefore, a complete medical history and physical examination usually are performed, together with laboratory tests. All concomitant medications are also recorded. Any special tests, assessments, or procedures relating to study endpoints are carried out at this visit or are scheduled, if not yet already done (53).

In CT that evaluated experimental medications, the baseline visit is concluded by dispensing by the first time the study medication, scheduling the next visit and arranging for any procedures needed for the next visit (53).

In this visit the SC has the role of explaining to the patient how to take the experimental medication, the importance of the compliance and accountability of study medication (the patients should always return the blisters/boxes/bottles of study medication) and how to fill the medication diaries, if they exist in the study.

I also provided support in several baseline visits of different studies.

Regular Visits

Following the baseline visit, the subject is seen by the investigator at intervals specified in the protocol which occur at determined time points from the date of the baseline visit (53).

These visits are intended primarily to monitor the progress of the subject and its tolerability regarding the study intervention. In each regular visit, a brief medical history and physical examination are undertaken and any adverse events or findings are sought. Subject compliance regarding medication is also generally evaluated since the subject was asked to bring the unused study medication to do its accountability. The regular visits are concluded by dispensing the study medication, scheduling the next visits and arranging for any procedures/tests necessary for the next visit (53).

In practice what I did as a SC in these visits is described below.

When a subject had a trial visit it was generally necessary contact him/her, a few days before or on the day before, in order to remember of the occurrence of the visit or to remember of other issues, such as remind the patient that needs to come in the fasted state to the visit.

Generally on the day preceding the study visit I prepared everything that was necessary to perform it. Therefore, to prepare a visit I first looked at the flowchart of the trial to check which procedures had to be performed. Then I pulled off the patient's folder of study cabinet and gathered together the following sheets: blank sheets to the investigator fill out with the description of the visit; a standard sheet, created by the SC, to record the vital signs; Interactive Voice Response System (IVRS) codes and IVRS sheets, if applicable; a sheet for the request of experimental medication to pharmaceutical services – the *prescription sheet;* a requisition, duly completed, if the collection of laboratory samples was necessary, and other sheets specific of

each trial and necessary to the visit, such as sheets to schedule ophthalmologic or magnetic resonance imaging exams. If there were laboratory samples, I also pulled off the respective laboratory kit and prepared the collection tubes (filled the labels of each tube with the required information and pasted the labels in the respective tubes) necessary to the visit of the next day.

Unscheduled Visits

Sometimes the patients develop complications and may need to be seen between scheduled visits. The reasons for, and findings obtained during unscheduled visits must be recorded as study data (53).

I provided support in some unscheduled visits, namely in the CT of Multiple Sclerosis conducted at the centre. In this disease the occurrence of relapses is common and therefore when a patient is participating in a CT and has a relapse, an unscheduled visit should be performed.

Final Visit/End of Treatment Visit

The final visit is the last visit of the trial wherein the subject is still receiving the study intervention. This visit includes essentially the same observations/procedures that the baseline visit in order to compare the outcomes of this visit with those of the baseline visit. Additionally, the same type of information collected at regular visits is obtained to cover the interval since the last regular visit (53).

At the end of the final visit, study intervention is ended and one or more study follow-up visits are scheduled (53).

Exceptionally, it is also necessary to perform a final visit when a subject ends the trial prematurely, e.g., because of intolerable side effects or other reasons. In this case, all attempts must be made to schedule the final visit with the subject in order to perform all the necessary observations/procedures. The completion of the final visit, even prematurely, is a way to guarantee that the data obtained from the subject until that moment may still be analysed and included in the results of the study (53).

I only provided support to one final visit.

Post-study Follow-up Visits

Subjects should be seen at least once after finishing their study participation to guarantee that they are not suffering any sequel that might be associated with their study involvement (53).

The post-study follow-up visits are generally scheduled at 1 week to 1 month after the final visit, depending on the possible duration of effects of the study intervention (53).

I provided support to three post-study follow-up visits.

Site Closure Visit

When the trial is completed or it is terminated early at the site, a SCV should be performed in order to the study be properly "closed". This cannot happen until all of the subjects have completed the course of the trial, were dropped or withdrawn. At the SCV, all the documents are verified to make sure they are in order, final Source Data Verification (SDV) is carried out, all the queries and follow-up on serious adverse events are closed out and the drug is reconciled and generally retrieved from the site for destruction (5,49).

Schedule of Subjects Trial Visits and Observations

The protocol must provide a schedule of subject visits, generally represented as a flowchart, with details about when these will be conducted and what information will be gathered at each visit. This section of the protocol is strictly followed by the study staff including the SC and is an excellent working tool (53).

It is important to specify the timing of the trial visits with a window of plus or minus a short number of days, if possible, to enable some flexibility in scheduling appointments (53).

The SC is responsible for ensuring that all subject visits are scheduled and performed at the right time within the window of each visit. If a visit is conducted out of its window, a finding is noted for the centre, which is not good for the statistics of the centre and its reputation.

Request of Study Medication

The request of study medication can be done via IVRS or Interactive Web Response System (IWRS).

The use of an IVRS or IWRS for management of CT has become very popular, especially for multinational CT. The IVRS or IWRS has the capability of functioning without human intervention, which makes worldwide access possible. For this reason, these systems are an ideal tool for central randomization and drug management in clinical research (17).

The IVRS is a voice support system that uses the telephone as the interface between the end-user and a central computer. To use the system the SC needs to dial a specific number (different for each study) which addresses the IVRS. Then a set of instructions and options is given by a pre-recorded voice (in any language) and the SC can select the desired option by pressing the keys of their telephone in order to receive the desired information (54,55).

The IWRS is the web-based equivalent of IVRS, where instead of the telephone, a secure webpage is used as the interface with the central computer, allowing the end-user to select menu options and to enter and receive data and instructions (54).

These systems allow several actions namely: patient screening and screen failure tracking, remote patient randomization and study medication assignment to subjects (55,56).

After the assignment of the study medication through one of these two systems it is necessary to fill in the *prescription sheet* with the information provided by the IVRS or IWRS system. This sheet has generally, regardless of the study, similar information. The first part of the sheet has the name

of the study; the screening or randomization number of the patient; the number of the visit or dose of study medication and the number of the kit(s) assigned. This information can be filled in by the SC. The second part consists of information about the study medication namely the batch number, the batch expiration date, the total volume of study medication prepared (in the case of infusions) and other information. This part is filled in by the pharmacist.

The prescription sheet must always be signed and dated by the investigator before being sent to the pharmaceutical services. In the CIC, the sheet is sent to the pharmaceutical services by e-mail. Afterward, the pharmaceutical services fill in the sheet and send by a designated person the requested medication along with a copy of the sheet. The original sheet is then sent to the pharmaceutical services.

Before I start using the IVRS and IWRS I received training from the senior SC who taught me how to register a new screening of a subject, to randomize trial participants, to assign the study medication, to register a screen failure in the system, among others.

Accounting of Study Medication Returned

Generally the accounting of the study medication returned by the subjects is not done by the SC but only by the pharmacist at the pharmaceutical services. However, in one study conducted at the centre, the SC also do the accounting of study medication since this information is necessary to fill in the CRF of the study.

Measurement of Vital Signs

At each study visit, and if necessary according to the flow chart of the study, I measured the vital signs of the patient, namely the blood pressure, heart rate, tympanic temperature, respiratory rate, weight and height.

Performing ECG

Some trials visits require the realization of one or more ECG. In the CIC, the SC are responsible for performing ECG in trial participants. I was instructed by the senior SC on how to deal with the electrocardiograph and how to perform an ECG.

In some CT, it is required to send the ECG performed to the central team of the study. In this case, the ECG is transmitted from the electrocardiograph to the central team through telephone network. This task is also a role of the SC.

I provided support in the realization of several ECG but only did one without help since only at the end of the training I felt confident to perform this procedure. On the other hand, I sent several ECG to the central team.

Processing Laboratory Samples

This activity can be divided into a number of sub-activities. First, I helped the laboratory technician, which withdraws the blood samples, by giving her the required tubes for the blood

collection. After the collection, I gently inverted the tubes according to the instructions presented on the laboratory manual specific for each study. Then, I transferred the tubes to the area where they would be processed, and waited to allow the clotting of the blood or centrifuged immediately, depending on the instructions of the laboratory manual. When the centrifugation was finished, and if necessary, I transferred the plasma/serum to the transference tubes and proceeded to the packaging of tubes for their transport. In some studies it was also necessary the preparation of smears.

Additionally to the blood samples, in some visits it is also necessary to collect a urine sample and send it along with the blood samples. In some visits of specific CT a urine dipstick test is also performed by the SC and the results recorded.

The samples can be sent to the external laboratories at room temperature, refrigerated or on dry ice. If the samples need to be shipped on dry ice it is necessary to request the sending of dry ice in advance, preferentially by fax.

Entry of Data into the CRF and Query Resolution

A CRF is a document on which the information, required by the trial protocol, about each trial subject is recorded. It can be a printed, optical or electronic document and its design vary from trial to trial. The data recorded on the CRF will be used to perform the statistical analysis of the trial (8,57).

In the end of each visit, the information collected according to the trial protocol during the same should be introduced in the CRF.

The SC is responsible for ensuring the integrity of the data introduced on CRF. However, errors inevitably happen during data entry, such as typographical, copying, coding or range errors. Typographical errors generally occur when someone is typing very fast. In the case of copying errors, these typically occur when the handwriting in the source document/paper CRF is not very legible what happens very frequently with the handwriting of doctors and really difficult the transcription of information. Coding errors can be made by the filling of CRF with given codes. Lastly, range errors happen when lower and/or upper limits of known values are exceeded when typing (17).

Therefore, to assure data quality, a system must be implemented to check and query all the introduced data. A data query is raised when exists missing, inconsistent, or illegible data (in case of paper CRF), or protocol deviations on CRF. The query resolution should be as soon as possible. Sometimes clarification is necessary and to do so the study monitor discusses with the SC the pending queries (58).

Data queries help to guarantee the quality of the data and the integrity of the study and therefore are an essential part of any study (58).

During my training I worked with several types of electronic Case Report Forms (eCRF) platforms namely: InForm™, RDC Onsite™, Medidata Rave™, Viedoc™, BioClinica Express™, among others.

I also worked with other platforms of data entry such as the QCAT™ platform. This platform is used for a trial conducted at CIC and in it are introduced, in PDF format, the neurological scales applied by the psychologists to the trial participants and the respective recordings, in mp3 format, of the scales applied.

Before I start working with these platforms I received training from the senior SC at CIC who taught me how to work with these systems and how to answer queries.

Activities of Data Entry

I also helped an investigator of the CIC with a database that he created and was developing. My help consisted in the introduction of data in the database.

Organization, Maintenance and Update of Study Files

Clinical studies generate vast amounts of paperwork, all of which must be stored during and after the studies.

The SC has the essential role of organizing, maintaining and updating study files at the centre, namely the Investigator Site File (ISF), the patient's folder and other folders specific for each study. Each study has its own documentation which is always very extensive and thereby is essential that a SC has good organizational and management skills.

Since I already had good organizational and management skills, this task was not difficult to me.

Control and Management of Study Supplies Stock

The control and management of study supplies stock is one of the responsibilities of the SC. It is necessary to check regularly: the number of kits available at the centre and its expiry dates, the number of boxes available to package the samples, the number of waybills available for sending samples, the existence of pipettes and sleeves to process the samples, among other material.

If there is lack of any of this material in the centre, the SC should order the necessary material through a specific form that is sent to the sponsor/CRO or laboratory of each clinical study (e.g., Covance, Quest Diagnostics, etc.).

Preparation and Sending of the Calendar for the Next Week

Every Friday a SC of the centre send a calendar to the pharmacy with the trial visits that will be performed on the next week and that need dispense of experimental medication by the pharmaceutical services.

Likewise, a calendar is sent to the study nurses with the trial visits for the next week that need nursing support. A calendar is also sent for the psychologists when the trial visits included scales applied by them.

Support to Monitoring Activities

The ICH/GCP guidelines, EU CT Directives and numerous national regulations demand that the sponsor/CRO monitor the progress of the CT at the sites where it is being conducted (49).

The overall aim of these periodic monitoring visits is to guarantee: that the investigators and their staff follow the GCP, local regulations and protocol; that the rights, safety and well-being of trial participants are being respected and that the data reported are complete, accurate, verifiable and reproducible (49).

The first monitoring visit should take place soon after the enrollment of the first few subjects in the trial. The next monitoring visits should be schedule based on the objective of the trial, the rate of enrollment and the quality of the data coming from the site (49).

During the monitoring visits, the study monitor should meet with the investigator to review any issues that need clarification or explanation and to consider any questions that may appear on the progress of the trial (49).

Additionally, the SC must be promptly available in these visits in order to support the study monitors. The SC can help through the retrieving of source documents, as required; query resolution and by making necessary corrections to the CRF; and by providing regulatory documents, as required (49).

The Journal Club

Every Wednesday at 8 am there is a meeting at CIC named “The Journal Club”, organized and presented every week by a member of the neurology group. The aim of these meetings is to provide additional medical and scientific knowledge to the group through the presentation of relevant articles in the area of neurology, namely the area of movement disorders, or video sessions to discuss clinical cases that are more complex and atypical than the cases of normal clinical practice. The SC of the centre were invited to always be present in these meetings, what for us it is a good opportunity to learn more about the diseases (e.g., PD) studied in the clinical studies conducted at the CIC.

Meetings of the Unidade de Farmacologia Clínica

Every two weeks on Wednesdays at 6 pm there is a meeting at UFC, with all the members of the UFC in which usually each sub-unit has the opportunity to share with the rest of the group their mission, objectives, work on a daily basis and ongoing projects. At each meeting the members of a sub-unit of the UFC make a presentation about the topics referred above. These meetings are a good way to acquire knowledge in other areas and to know the work that was being developed in the various sub-units. Sometimes people working in other organizations are also invited to make presentations.

ALN-TTR02-003 and ALN-TTTR02-004

During my internship at CIC I worked in almost all the clinical studies ongoing at the centre, helping in everything what was needed. However, in the CT ALN-TTR02-003 and ALN-TTR02-004,

ongoing at the CIC, I had a participation more active and autonomous, providing support to all the trial visits.

The ALN-TTR02-003 is a phase 2, multicentre, open-label, extension study which aims to evaluate the long-term safety, clinical activity and pharmacokinetics of ALN-TTR02 (Patisiran) in patients with FAP who have previously received ALN-TTR02 (59).

The ALN-TTR02-004 is a phase 3, multicentre, randomized, double-blind, placebo-controlled study which aims to evaluate the efficacy and safety of ALN-TTR02 (Patisiran) in patients with FAP (60).

My participation as SC in these two studies consisted of: preparing and accompanying trial visits, giving support to study team, introducing data in CRF and query resolution, processing and shipping of laboratory samples, maintaining of study files and managing of study supplies stock.

The study medication (ALN-TTR02) of these two trials is administered by intravenous infusion by a study nurse. At every trial visit a SC gives support to the study nurse in several tasks namely: measurement of vital signals, withdraw of blood samples and collection of urine samples, record of all the necessary information in the checklist (e.g., time at which vital signs were measured, blood samples were withdrawn, study medication was administered, etc.) and clarification on any questions about study procedures.

The REGISTRY Study

REGISTRY is a prospective OS without experimental treatment. It is a multicentre and multinational study and is integrated into the Huntington Project. This project is a global collaboration which aims to find treatments for HD (61,62).

In OS researchers do not try to influence participants or the surroundings (63). OS draw inferences about the effect of an exposure or intervention on subjects, where the assignment of subjects to groups is observed rather than manipulated (e.g., through randomization) by the investigator (64). The purpose is to observe and collect data on characteristics of interest without influencing the participant, environment or a disease course (63). Therefore, observational research involves the direct observation of subjects in their natural setting (64).

When an OS involves a medicinal product, this is prescribed in the usual manner in accordance with the terms of the marketing authorisation once the assignment of the patient to a particular therapy strategy is not influenced by a trial protocol, but by the current practice. The prescription of the medicinal product is also clearly separated from the decision to include the patient in the study and the subjects should not be submitted to any additional evaluations. The data collected should be analysed by epidemiological methods (31).

Registry is sponsored by the High Q Foundation, a non-profit organization that supports various research projects which aim to find treatments for HD (62).

The goals of REGISTRY are to:

- Collect natural history data in a large number of HD mutation carriers and subjects that are part of a family with the disease;
- Relate clinical features with genetic factors, data derived from the study of body fluids (blood and urine) and imaging data;
- Streamline identification and recruitment of participants for CT;
- Plan for future research studies;
- Develop new measures to track and/or predict HD onset and progression, along with the improving the existing tools (61,62).

During my training I provided support in several activities within the framework of this study. The description of the activities developed is presented below.

Conduction of Study Visits

I provided support to some study visits and conducted a few. Since the Registry is an OS, there is no study medication available and therefore the study visits are easy to conduct. The Registry subject's visits are only annually and at each visit there is collection of blood and urine samples; the participants and companions perform some self-completion questionnaires; and the participants are seen by a psychologist who performs some neuropsychological assessments and by the investigator of the study who does the clinical evaluation.

Creation of a Study Database

I created along with another trainee colleague a database for the study Registry. The database was created in Excel and comprises information about the study participants which is essential to a good organization and management and eases the tasks of the study.

Site Monitoring Visit

I had the opportunity to go to a site monitoring visit of the study REGISTRY with a SC of the centre who is also doing monitoring activities within the framework of this study. This SC is responsible for monitoring all sites in Portugal which are conducting the study because the CIC is the Portuguese Language Coordinator Site, in other words, the CIC is responsible by the coordination and monitoring of the study in Portugal.

The visit was to the Hospital de Santo António dos Capuchos in Lisbon.

The site monitor visit lasted one day and during the day we verified if:

- ICF were duly signed and dated;
- all required source documents were available on site;

- the information on the source documents corresponded to the information introduced on the CRF;
- the information introduced in the CRF made sense and was consistent;
- and issued queries.

We had some limitations in this site monitor visit since sometimes it was hard to find in the source documents the information (e.g., medication taken by the patient) that was described on the CRF.

The accompaniment of this site monitoring visit was a very enriching experience, since it allowed me to see in practice the role of a study monitor, the tasks carried out by the study monitor and how these activities are done. I also gave support to the site monitoring visit and therefore I could perform the tasks of a study monitor.

Good Clinical Practices Course

In the last day of my curricular training I attended to a GCP course. It was a one-day course and covered several topics, namely: introduction to the GCP and its principles; legislation and regulatory aspects; clinical study protocol; essential documents; responsibilities of the investigator, SC, monitor, CRO and sponsor; safety and adverse event reporting and practical aspects of conducting clinical studies.

Any professional working in the clinical research area must have a GCP course in his/her training, which should be updated preferably every two years.

Most of the topics covered in this course were already of my knowledge, but this course was important to assure and certify my knowledge in GCP.

4.2. Sub-Unidade de Bioestatística e Metodologia

I started my internship at SBM on November 11th and lasted until January 9th. Since I have a limited background in biostatistics and there was a person responsible for the submission of scientific articles and development/submission of applications for scientific projects, my internship was focused primarily in activities of clinical data management and medical writing.

During these two months of internship I did some activities related to the projects that were ongoing in the sub-unit.

My first activity was related with the project SENSE-PARK, a project directed towards PD. The team of the SBM was writing the last articles about the results of a study that had been conducted in the Hospital with the SENSE-PARK system and I was asked to read various articles about systems similar to the SENSE-PARK in order to enrich the methods, results and discussion of the articles that were being written.

Currently, the assessment of the progression of PD in each patient is based on clinical appointments at specific time points. This approach does not reflect the real condition of patients

in daily life and gives only a snapshot of the disease. Therefore, to objectively measure the disease progression is necessary the implementation of a continuous objective measurement (65). This accurately measurement of the disease can result in the development of personalized treatment plans that will allow a better management of the disease by the patients on a daily basis (66).

The SENSE-PARK project is funded under the European Community's Seventh Framework Programme and aims to approach the present limitations in measuring accurately PD (65,67). The SENSE-PARK system consists of a set of devices that allow continuous assessment of motor symptoms of patients with PD on a daily basis and in their home environment. Wearable devices gather the information and detect fluctuation in motor symptoms. The system also includes tests to evaluate the non-motor symptoms (68).

The symptoms domains that the SENSE-PARK system is capable of measure are: gait, tremor, balance, bradykinesia, sleep and cognitive function (68).

My second activity was to organize and manage a clinical database obtained from the SVIG. This clinical database contained data characterizing ADR, reported to the INFARMED, in which the suspect or interacting drugs were antithrombotic drugs (anticoagulants and antiplatelet drugs). I also organized and managed a clinical database with data extracted from the study SENSE-PARK.

During this internship I also had the opportunity to see clinical databases in Excel format with the data collected at a specific OS through the CRF and see how this information is subsequently validated and treated. This allowed me to know the viewpoint of the data manager and realize the importance and the role of each data that I introduce in the CRF as a SC.

Lastly, I worked with a Doctor who was doing his PhD. I helped him writing an article about the pattern of major bleeding events in patients treated with oral anticoagulants and also gave some support in an article about gastrointestinal bleeding.

Treatment with anticoagulants is associated with an increased risk of bleeding despite the proven benefits of this therapy in prevention/treatment of cardiovascular diseases (69). The occurrence of events of anticoagulant-related bleeding results in mobility, mortality and significant costs (70).

Anticoagulant-related bleeding is a common and critical drug-induced illness (69). Thus, it is extremely important to determine the pattern of major bleeding events associated with anticoagulation treatment in order to manage and prioritize interventions to prevent this risk.

The writing of this article allowed me to get knowledge in a new area, the area of the oral anticoagulants, including the traditional and new oral anticoagulants, and understand its limitations and associated risks.

During my internship at the SBM I attended to an Intensive Course in Pharmacovigilance organized by the URFLVT and held at Hospital de Santa Maria. The topics covered in this intensive course were ADR mechanisms and risk factors, benefit-risk assessment, studies in pharmacoepidemiology, methods of drug safety monitoring, spontaneous reporting of ADR,

systems of imputation and causality assessment, ADR by system/organ (neuropsychiatric, cardiovascular, hematologic, dermatological, gastrointestinal, renal, hepatic) and ADR in paediatrics.

In these two months of training at the SBM I continued providing support to the CIC whenever necessary. I provided support mainly in the ALN-TTR02-003 and ALN-TTTR02-004 through the preparation and support of subject trial visits, the processing of laboratory samples and data entry in CRF.

4.3. Unidade Regional de Farmacovigilância de Lisboa e Vale do Tejo

I started my internship at URFLVT on January 12th and finished it on 13th March. In my first two weeks at the Unit I read various materials essential for my integration and contextualization.

My first activity was to read some crucial chapters, for my work at the Unit, of the book "Farmacovigilância em Portugal", published by INFARMED.

Reading this book gave me an excellent overview of:

- the historical aspects of pharmacovigilance in a comprehensive manner;
- the organization of the Portuguese Pharmacovigilance System;
- the monitoring of ADR;
- the safety periodic monitoring (management and evaluation of renewals of Marketing Authorizations and of Periodic Safety Update Reports (PSUR));
- the causality assessment;
- medical and pharmacological terminologies (Medical Dictionary for Regulatory Activities (MedDRA) and Anatomical Therapeutic Chemical (ATC) classification system);
- the main ADR that occur in each system/organ and the mechanisms involved in its occurrence (cardiovascular, haematological, hepatic, gastrointestinal, neuropsychiatric, renal, skin and respiratory ADR).

I also read the applications of the Unit to the public contests, the collaboration protocols between the Unit and the INFARMED and the Activities Reports of the Unit of the first and second semester of 2014.

Then, I read the Quality Manual which allowed me to know and understand the Quality Management System implemented at the Unit. The Quality Manual gave me an overview of the documental structure, the procedures and work instructions in force in the Unit and the established responsibilities. With my work at the Unit I understood the importance that a Quality Management System has for an institution. A Quality Management System ensures that a particular activity is always performed in the same way regardless of the operator and that the result of this activity is always the same. It is intended to prevent errors/deviations and it should aim continuous improvement.

Lastly, I read the Good Pharmacovigilance Practices (GVP) giving special relevance to Module VI – Management and reporting of adverse reactions to medicinal products and to Module VII –

Periodic safety update report. The GVP provide practical measures to ease the performance of pharmacovigilance according to the legislation and it applies to MAH, the EMA and NCA in EU Member States (46).

By reading all this material I got to know the goals, mission, vision, values and the services provided by the Unit and how it works. These two weeks of integration and contextualization also allowed the consolidation of the theoretical knowledge that I already had in the pharmacovigilance area and allowed the acquisition of new knowledge.

During my training at URFLVT I attended to a conference at Faculdade de Farmácia da Universidade de Lisboa about "The European Medicines System" presented by Dr. Anabela Marçal (Head of Compliance and Inspections Department, EMA). The themes addressed in this conference were: the European Medicines Regulatory System; the role of EMA and NCA; the marketing authorization procedures existing in the EU (centralized, mutual recognition, decentralized and national procedure) with special focus on the centralized evaluation system; the Co-ordination Group for Mutual Recognition and Decentralized Procedures – Human; the Common Technical Document; the marketing authorization application types (complete, generic medicinal products, informed consent, etc.); the appeal and referral processes and the conditional approval and exceptional circumstances.

I also attended a class given by one of the pharmacists of the Unit to students of medicine at Hospital de Santa Maria. The class addressed themes such as the concept of generic medicine and bioequivalence, medicines with narrow therapeutic index, the establishment of prices of the generic medicines, the reference pricing system, the reimbursement in the National Health System and the medical prescription.

My main activity during the internship at the URFLVT was the handling of spontaneous reports of ADR. This handling comprised the reception, validation, classification and processing of spontaneous reports of ADR.

Additionally, I wrote case narratives, causality reports and causality letters to attach in the ADR Portal and also did follow-up of reports. The causality letters are also sent to the reporters.

The process of the handling of a spontaneous report is described below.

In pharmacovigilance, a spontaneous report concerns only one case which is constituted by a patient, an identifiable reporter, at least one suspected ADR and at least one suspected drug. The reports are received and collected in accordance with this principle (11).

Whenever a spontaneous report is received at the URFLVT, is necessary to verify the following items: if the report comes from the Unit's action area, if the suspected drug is in fact a drug, if there is a duplicate of the concerned report, if the report has the four minimum criteria to be validated and what is the consistency of the report.

For a report to be considered valid it needs to contain the following minimum information:

- an identifiable reporter;

- an identifiable patient (initials or patient number and/or gender and/or age; the information should be as complete as possible and the patient's name should not be reported);
- at least one suspected ADR;
- at least one suspected medicine/active substance (11).

This minimum information is commonly called minimum criteria. It must be available for:

- the attribution to the report of an identifying alphanumeric sequence of the SNF (the international number of the report);
- the registration of the report in the SNF database;
- the report become an available source of safety data for the generation of signals (11).

All necessary efforts should be undertaken to obtain this minimum information (11).

If a report does not have the minimum criteria, especially the reports about serious and/or unexpected ADR, it should be made attempts to obtain immediately all the required additional information from the reporter or from another available source (11).

Throughout the technical and scientific evaluation of the report, namely during the causality assessment, it is also often necessary to contact the reporter in order to obtain additional information (11).

Additionally, in certain cases it is necessary to obtain further information in relation to long-term consequences of the ADR (11).

The detection of duplicates is an extremely important step. Some ADR, especially the serious and/or unexpected, are reported to the competent authority by more than one source (e.g., a physician and a pharmacist) and by more than one route (e.g., direct sending of the reporting form by a health professional and sending via MAH of the Council for International Organizations of Medical Sciences (CIOMS) model) (11).

It is also crucial that the information on a specific spontaneous report is sufficient to enable the detection of duplicates. The registration of the information of each report in the database is only made after a duplicate detection process. This is done through the various fields of the reports, namely through the information regarding minimum criteria (11).

After these steps, the report is validated. All the sheets of the report are signed and dated with the date of reception. Then the report is scanned and saved in the internal network of the Unit. A copy of the report is printed and attached to its original.

The Unit has seven consecutive days, counting from the day of receipt of the report, to handle the report and send it to the SVIG. The date on which the report should be finalized is registered in the online calendar of the Unit.

The information on the spontaneous report in the paper reporting form is then transcribed to the ADR Portal. The Unit has also a database in Excel format with information about all the spontaneous reports received at the Unit since its creation. Whenever a new spontaneous report is received, this database needs to be filled.

If the spontaneous report is submitted by the reporter through the online reporting form of the ADR Portal, the spontaneous report is accessed by the team of the URFLVT through the back office of the ADR Portal and then its information is validated and printed.

The information on the spontaneous report needs to be coded to be inserted in the ADR Portal. The signals and symptoms, diseases, diagnostics, therapeutic indications, research results, medical and surgical procedures and the family, social and medical history are codified in by the MedDRA. The medicines are classified by the ATC classification system (11,12).

For all spontaneous reports (serious and non-serious), it is made a contact with the reporter, via e-mail or by telephone, in order to obtain or confirm data about the case and to attest that the reporter really exists. In reports received by telephone, this contact is only necessary when there is still outstanding information. The new data obtained is recorded in the printed copy of the report and is also added to the ADR Portal.

After this contact with the reporter, the case narrative is written and all the information previously introduced in the ADR Portal, relative to that specific report, is reviewed once again by a second person (one of the pharmacists). This step is done within the scope of the quality system implemented in the Unit as a validation/ quality control step aiming to reduce the rate of errors.

The ADR also need to be classified as “expected” or “unexpected”. This classification is performed based on the information presented in the SmPC, with clinical judgment whenever necessary. The clinical judgment is particularly necessary in the cases where the nature, intensity or evolution of the reported ADR differ from that described in the SmPC (11).

“The case narrative should serve as a comprehensive, stand-alone “medical report” containing all known relevant clinical and related information, including patient characteristics, therapy details, medical history, clinical course of the event(s), diagnosis, adverse reactions and their outcomes, relevant laboratory evidence (including normal ranges) and any other information that supports or refutes the suspected adverse reactions (40, p.37).”

It should contain, in the order listed, the following information:

- The minimum criteria and relevant data (summary of the case);
- Description of the onset and development of the ADR;
- Relationship between the drug and the ADR;
- Treatment of the ADR;
- Other relevant data on the evaluation of the ADR;

- ADR evolution.

After the finalization of the case narrative, the report is sent from the backoffice of the ADR Portal to the SVIG and the international number of the report is generated.

In the follow-up of reports, the additional information should be added to the case narrative preceded by the date on which the information was obtained, with the reference of “follow-up”. The last information of the follow-up should be the evolution of the ADR, even if it is equal to the evolution of the initial case.

When new information is obtained within the time frame of seven days to handle the report, this information is not considered a follow-up. In other words, new information is only considered as a follow-up when the report has already been handled and sent to the SVIG.

The Unit has thirty days to perform the causality assessment and insert it in the database. In the URFLVT the causality assessment is carried out by global introspection, but other methods can be used (12).

The causality assessment is performed by the physician who acts as clinical coordinator of Unit. However, the two pharmacists who work at the Unit also give their opinion about the causality assessment.

The result of the causality assessment is expressed in degrees of probability, based on the scale of degrees of probability of WHO: certain; probable/likely; possible; unlikely; conditional/unclassified and unassessable/unclassifiable (11,12). The result is sent to the reporter by e-mail or post through the causality letter.

The causality letter is a document which is intended to thank the reporter for their contribution to the SNF, to inform the reporter of the international number attributed to the report, to describe if the ADR(s) reported is/are expected or unexpected and to inform about the causality assessment attributed to the spontaneous report.

Subsequently, the reports of ADR loaded in the SVIG are processed in the INFARMED through a phased system of receipt, validation, verification of duplications, coding and registration in databases, technical and scientific analysis with causality assessment and detection of problems, whose objective is the generation of signals (11).

In the whole process is ensured the confidentiality of patient, reporter and MAH data (11).

The access to reports, to the database and to results of research and analysis conducted is restricted. Search results to internal customers of INFARMED or external customers are always provided maintaining the anonymity of patients and reporters involved (11).

The signals generated by a spontaneous reporting system provide different types of suspected drug safety problems. These problems include the detection of new ADR; suspicions of change of frequency of ADR already known; new drug interactions or new drug interactions between

medications and other health products or foods; quality or therapeutic inefficacy problems and inherent problems to the way of use of the medicine (11).

The meticulous process of technical and scientific evaluation of reports in order to detect unknown security problems to date corresponds to the process of signal generation (11).

In addition to all these activities, I also performed activities of medical writing at the Unit. I helped in the writing of an article to submit to a scientific journal (Pharmacoepidemiology and Drug Safety). The article had as a source a master's thesis written by a physician in order to complete their Medical Degree. The theme of the master thesis, and therefore of the article, was the characterization of ADR with neuropsychiatric clinical manifestations reported spontaneously to the Portuguese Pharmacovigilance System in the greater Lisbon area between January, 2006 and December, 2012.

5. Discussion

In this curricular training of ten months, I developed activities in several areas of the drug sector namely clinical research, pharmacovigilance, medical writing and data management. This diversity of activities was very important and enriching, since it allowed me to experience different areas and to discover my preferences and in what I would like to work in the future. Besides this, I gained several competences and confidence to work in any of the areas mentioned above.

The internship at the CIC was the longest, six months, and the main focus of the entire curricular training. The CIC is a clinical research centre with sixteen years of experience in clinical research and is considered a centre of excellence in the area of neurology in Portugal. Therefore, it is the ideal centre to learn, grow professionally and become autonomous. The CIC has a competent, motivated, dedicated and proactive team of health professionals that invest the necessary time in the conduction of the clinical studies. This team is a key piece and a major contribution for the success of the centre. The CIC has qualified people working full time in the conduction of the clinical studies, two senior SC; the investigators of the CIC are always trying to recruit new patients and truly collaborate and help the SC and the whole team is in tune and works very well together. The CIC has also high rates of patient retention in clinical studies and low rates of dropouts. I believe that if there were more centres in Portugal similar to the CIC the number of clinical studies conducted at our country could increase and its quality could be improved.

The SC have various responsibilities and carry out several different activities. Additionally, in this centre the SC perform activities that generally are not carried out by them in other clinical research centres in Portugal, such as measurement of vital signs, performing ECG and processing of laboratory samples. Because of this particularity I liked even more of my role as SC in the CIC, since I could follow the entire process of the study visits since its preparation, on the day before the visit, until the introduction of the data in the CRF, after the study visit.

At CIC, the SC have several activities to do every day and for different clinical studies since there is usually more than one study visit per day. The SC have also the responsibility of ensuring the rights, safety and well-being of study subjects and the credibility of clinical study data. Thus, a SC should have several soft skills, namely good ability to work in team, good time management, organizational, communication and problem-solving skills and proactivity and responsibility.

I already had these skills since some are qualities that characterize me (e.g., good organizational skills and responsibility) and others were developed during my academic training (e.g., good time management and communication skills and proactivity). However, my internship at CIC allowed me to improve these skills on a daily basis.

The description of the day by day of a SC demonstrates that these soft skills are really very important to do a good work as SC. Every day I had several activities to do and I had to manage my time and prioritize activities. I also had always many documents from different studies to fill in, archive or to give to the investigators to sign. It is very important do not lose any document and archive them in the right place to be easy to retrieve these documents whenever necessary. Every day things with which we are not counting happen (e.g., a patient calls and warns that

cannot come to the trial visit and the SC needs to cancel everything and reschedule). Thus, it is very important to have problem-solving skills for these unexpected situations. As SC, I also had to communicate with various healthcare professionals (e.g., physicians, nurses, pharmacists, psychologists, etc.), other professionals from the pharmaceutical companies (e.g., study monitors, auditors, etc.) and patients and its relatives. It is important to adapt our discourse to every type of person and to be clear and precise. Besides this, each person has its own personality and character and I had to learn to deal with it. Lastly, a SC has a position of great responsibility. Any error (e.g., mix the blood samples of different patients or perform a study visit out of the window) can compromise the patients' well-being, the credibility of the data and/or the reputation of the centre. The example of mixing blood samples of different patients is a good example because sometimes we had two visits of the same study with different patients and I had to process all the blood samples in the same space and sometimes at the same time. Therefore, it was very important to label every tube correctly and be extremely organized and cautious. During my training I felt how important is to be responsible in our work and I always gave my best in everything I did.

During my internship at CIC I had contact with several protocols with different study designs, procedures and levels of complexity; different sponsors/CRO and different neurological diseases. This variety was very important because it allowed me to gain a transversal knowledge in the clinical research in the area of neurology.

At CIC, the SC have a constant and strong contact with the study subjects. The SC perform the majority of the procedures of each study visit and generally even when the SC do not perform a procedure (e.g., withdraw blood samples), they provide some type of support to the procedure. The SC are also the responsible person for guiding the patient during the visits and for explaining to the patient how to take the medication and how the return the medication, when it will be the next visit and what procedures will be necessary for the next visit.

The major difficult that I felt at CIC was this contact with the patients of the clinical studies. The studies conducted at CIC have as therapeutic indication neurological diseases. The majority of these diseases cause high levels of morbidity and in an advanced stage, the death. Sometimes it was difficult to me to deal with these patients seeing its advanced stage of disease and knowing how its disease is going to progress. At the start, it was also difficult to make a conversation when I was with the patients and to create a relationship with them, but over time this process becomes more natural. In my opinion, I should have had a discipline at the University that had prepared me to deal with patients, diseases and complicated situations. Despite these difficulties, I consider that the contact with the patients is a very interesting and challenging part of being SC and with the daily practice these difficulties were successful overcome. On the other hand, it is very rewarding to know that we can help these patients providing them with new and innovative therapies. This is one of the reasons whereby I like so much of the role of SC. The clinical research area allows to offer new and innovative therapies to patients that have few or even any therapeutic options. This is exactly what happens with the majority of the neurological diseases that have only symptomatic treatments but no cure for the disease.

At the first weeks it was also difficult to manage so many activities without forgetting anything. To help me with so many activities I had a notebook where I wrote what I needed to do every day and the new things that I learnt at CIC. The CIC had also available an agenda where everything that was important was written. This was a very good tool of work. Over time, things have become more natural for me and I started to use less times my notebook. However, the agenda was essential to organize my day and time and I consulted it every day. The method of work adopted at the centre was also a good help to organize my day. The day at the CIC started always early, at 8 am. Generally, in the morning the study visits were conducted which included the clinical evaluation of the study participants, the collection and processing of biological samples, the request of study medication, among other procedures. At the afternoon the biological samples were sent to the external laboratories, the data collected at study visits were introduced in the eCRF, the pending queries were solved, the study visits for the next day were prepared and other procedures requiring more work desk were done.

During my internship at CIC I also had the opportunity to go to a site monitoring visit. This was a one day experience but it was very important since it was the first contact I had with monitoring activities and allowed me to try new activities, such as SDV and issue of queries.

As SC, I was not so involved in the process of implementation of the CT at the centre which includes the feasibility phase, qualification and site initiation visits, the submission of the CT to the competent authorities and discussion of the trial financial contracts. There were several reasons for this, namely my internship at CIC was only of six months and this period was divided in three months in 2014 and three months in 2015. Three months is a very short period of time to follow the entire implementation phase of a CT. Because of this I did not follow the entire implementation phase of a specific CT but I could see and follow some steps of this implementation phase (e.g., I was present in a SIV) in different CT. At the CIC, the senior SC were responsible for the implementation phase of CT but they explained to me all the important steps of this process.

It is important to highlight that my bachelor's degree in Biomedical Sciences and my master's degree in Pharmaceutical Biomedicine provided me an excellent background in the area of health sciences and in all phases of medicines life cycle. More important, my academic training provided me with important research tools. Even when I did not know something or I had doubts during this curricular training I knew how and where to search the information that I needed.

My academic background was also excellent in the clinical research area and this knowledge facilitated my adaptation and helped me in the role of SC. However, there are things we can learn only in the practice (e.g., how to process and send laboratory samples) and whenever I had doubts or questions I always questioned the senior SC. At CIC, I had to work with several softwares and equipments with which I had never worked, such as the different eCRF platforms, ECG machines, centrifuges and even the photocopier and the fax machine. Despite this, I consider that my adaptation was fast and in a short period of time I became familiar with the clinical studies protocols, its procedures and with the dynamic of the centre. The senior SC were crucial for the success of my training at CIC. They explained to me everything I need to know to carry out

my activities as SC and were always available to answer my doubts. They were also essential for my successful integration in the team of the CIC.

During my bachelor's degree in Biomedical Sciences I studied several neurological diseases, namely Alzheimer's Disease, PD, HD and FAP and this knowledge helped me to better understand the trials conducted at CIC. However, at the start of the training, I also had to study other diseases over which I had no knowledge, e.g., Multiple Sclerosis and Epilepsy.

Regarding the research in the area of neurology there is no doubt that this is a really complex research area. It is well known that few drugs (on average 12%) entering CT will be approved for human use. In the case of central nervous system drugs the rate of successful development is even lower (on average 8 %) when comparing with other therapeutic areas. Besides this, half of these failures occur late in development (71).

The other four months of my curricular training took place at the SBM and at the URFLVT. Although the main focus of my internship was the coordination of clinical studies, these four months at the SBM and at the URFLVT were an asset for my professional training and for this reason these experiences are valued throughout this report.

The internship at the SBM allowed me to work with clinical databases and write a scientific article.

My experience as data manager with clinical databases was short but it allowed me to see and understand the viewpoint of the data managers and the other side of the clinical studies. Additionally, I managed the clinical databases in Excel which allowed me to gain more experience with this programme.

The writing of a scientific article in the cardiology area was a challenge for me. Until this training, I had never written a scientific paper but I always wanted to try medical writing since it is a working option in the future. I also had little background in the field of oral anticoagulants and therefore, I had to search several articles about this topic in the PubMed and read them. In the end, this activity improved my writing skills and my knowledge about oral anticoagulants, including its advantages and risks.

I also gave some support in an article about gastrointestinal bleeding that was successfully published in a scientific journal. This publication was a great pride for me and I hope the article I wrote has the same success.

The internship of two months in the pharmacovigilance area was an excellent opportunity to know and to understand how a Regional Pharmacovigilance Unit works in practice and to carry out the activities undertaken daily at the Unit. It allowed me to complement my theoretical knowledge acquired at University and to understand much better the role and work of the pharmacovigilance in the assurance of the drug safety. This training also allowed me to see all the path of the spontaneous reports since the reporter until the NCA. The pharmacists who work at the URFLVT always tried to explain to me how the pharmacovigilance department works in the pharmaceutical industries and its connection with the work done at the Regional

Pharmacovigilance Units/NCA. This viewpoint is very important if I want to work in the future in the pharmacovigilance department of a pharmaceutical industry.

The URFLVT has an excellent quality management system implemented and therefore each task performed at the Unit is described in procedures and working instructions. These documents helped me to perform accurately the tasks of the Unit at the first times. At URFLVT, I also had to work with softwares with which I had never worked, such as the ADR Portal and the dictionary MedDRA.

During these two months I felt some difficulties. The first main difficulty was the codification, of ADR reported, with the medical dictionary MedDRA. The ADR codified and inserted in the ADR Portal should be as similar as possible to what the reporter wrote on the original spontaneous report. However, sometimes the reporter describes the ADR in a hard way to codify and standardize scientifically (especially reports from patients) or the exact term reported does not exist in the MedDRA and is necessary to find a medical synonym. With time and practice this task has become easier for me. The second difficulty I felt was related with the writing of the scientific article. The article that I wrote only could have a maximum of 3000 words to be accepted by the scientific journal, but the master thesis was 63 pages. Thus, it was difficult to me to select the important information for the article. The pharmacist at the Unit responsible for the writing of the article gave me an excellent help and told me the topics that I really should cover in the article and the topics that were not so important. The writing of this article improved my synthesis and writing skills and allowed me to learn how a scientific article should be written and formatted in order to be published.

During the curricular training I also had the opportunity to participate in some courses, namely the Intensive Course in Pharmacovigilance and the GCP Course, and in a conference and a class. These extra activities complemented my knowledge and enriched my resume.

To sum up, this curricular training exceeded my expectations that were already high and demanding. All of my primary and secondary objectives, established before the start of the curricular training, were achieved with the exception of the writing of a scientific paper related to the area of clinical research. Although I did not achieve this specific objective, I consider that the other activities of medical writing performed, by me, offset this shortcoming.

6. Conclusion

This curricular training allowed me to participate in various projects in three different sub-units (CIC, SBM and URFLVT) and to experience different work environments. Each day, during these ten months, was a new opportunity of learning, a new opportunity of improving my soft skills and a new opportunity of becoming a more complete professional. Each day was also a new challenge that I tried to overcome giving my best.

This was a multidisciplinary training which enabled the establishment of a bridge between the academic world and the working world. It was a great experience which marked the beginning of my professional career and enabled my professional and personal growth. During these ten months I had the opportunity to work and learn with professionals that have several years of experience and therefore, this interaction enabled me to acquire and develop my soft skills, competences and working methods.

The realization of trainings during the master's degree is an excellent way to prepare students for the working world, giving them important competences and experience that are going to be valued by the job market.

Regarding the role of the SC, in the internship at CIC I really understood how the work of the SC is crucial for the successful conduction of a CT. I cannot even imagine how CT can be conducted with quality and rigor without this specialized professional. The PI and other health professionals collaborating in the CT already have their profession (e.g., physicians, nurses, physiologists, etc.) and therefore do not have the availability required to manage a clinical study. Several activities of the CT require a lot of time, such as the introduction the data in the eCRF, the resolution of queries and the management of all the documentation. Additionally, over the years CT have become increasingly complex with the increase of procedures and bureaucracy. Thus, is crucial to have qualified people working full time in the conduction of the CT.

I really like the experience as SC because at the end of the day I felt that I was contributing to bring new and innovative medicines to the market and help all people who suffer from neurological diseases. The internship at the SBM and the URFLVT enriched the curricular training, allowed me to experience new areas and complement my academic background and opened new career opportunities for me.

This internship report aims to describe my curricular training of ten months; however I would like to highlight that is impossible to truly represent in a document all the work done by me and all my effort and commitment during this period of time.

During the ten months of curricular training I had several activities to do, namely the daily work at the hospital; the exams, assignments and the writing of this report; and other extra activities. Sometimes it was difficult to manage my time and do so many activities but I overcome these difficulties, developed my time management and organizational skills and now I am a more proactive and autonomous person. Besides this, I achieve all the primary objectives defined at the

starting of the training. Regarding the secondary objectives, I only did not achieve one but I did other activities during the training which offset this gap.

Finally, I would like to thank to all the members of the UFC team that invested in my professional formation and believed in my work and capacities, depositing their trust in it.

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